A | BOX SEQ

Please type a plus sign (+) inside this box → [+]

PTO/SB/05 (4/98)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office U S DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C F R § 1 53(b))

Attorney Docket No.	NMEDP001-2
First Inventor or Application Identifier	Snutch, Terry P.
Title	Novel Human Calcium Channels and...
Express Mail Label No.	EL362857074US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents

ADDRESS TO: Box Patent Application
Washington, DC 20231

1. [✓] * Fee Transmittal Form *(e.g., PTO/SB/17)*
(Submit an original and a duplicate for fee processing)

2. [✓] Specification [Total Pages 31]
(preferred arrangement set forth below)
- Descriptive title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings *(if filed)*
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

3. [✓] Drawing(s) *(35 U.S.C. 113)* [Total Sheets 4]

4. Oath or Declaration [Total Pages 3]
a. [✓] Newly executed (original or copy)
b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
i. [ ] DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

** NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).*

5. [ ] Microfiche Computer Program *(Appendix)*

6. Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
a. [✓] Computer Readable Copy
b. [✓] Paper Copy (identical to computer copy)
c. [✓] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [ ] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* [✓] Power of Attorney
9. [ ] English Translation Document *(if applicable)*
10. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
11. [ ] Preliminary Amendment
12. [✓] Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
13. [✓] * Small Entity Statement(s) *(PTO/SB/09-12)* [ ] Statement filed in prior application, Status still proper and desired
14. [ ] Certified Copy of Priority Document(s)
(if foreign priority is claimed)
15. [ ] Other: .....

16. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment.*

[ ] Continuation [ ] Divisional [✓] Continuation-in-part (CIP) of prior application No. 09 / 030,482

Prior application information. Examiner Basi, N. Group / Art Unit 1646

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

[✓] *Customer Number or Bar Code Label* *(Insert label here)* 021121 PATENT AND TRADEMARK OFFICE or [ ] *Correspondence address below*

Name					
Address					
City		State		Zip Code	
Country		Telephone	+1 970 668-2050	Fax	

Name (Print/Type)	Marina T. Larson, Ph.D.	Registration No. (Attorney/Agent)	32,038
Signature	Marina T. Larson	Date	

Burden Hour Statement This form is estimated to take 0 2 hours to complete Time will vary depending upon the needs of the individual case Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

Oppedahl & Larson

Applicant or Patentee: SNUTCH ET AL Attorney's Docket No. NMED.P-001-2
Serial or Patent No.: TBA Filed or Issued: HEREWITH
For: NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am
( ) the owner of the small business concern identified below:
(X) an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN NeuroMed Technologies Inc.
ADDRESS OF CONCERN ~~3963 W. 24th Avenue~~ 400 - 601 West Broadway, Vancouver, Canada ~~V6S 1M1~~ V5Z 4C2

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the above-captioned invention which is described in

(X) the specification filed herewith
( ) Application Serial No. _____, filed _____.
( ) Patent No. _____, issued _____.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *Note: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____
ADDRESS _____
( ) INDIVIDUAL ( ) SMALL BUSINESS CONCERN ( ) NONPROFIT ORGANIZATION

NAME _____
ADDRESS _____
( ) INDIVIDUAL ( ) SMALL BUSINESS CONCERN ( ) NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Natalie Dakers TITLE Chief Operating Officer
ADDRESS OF PERSON SIGNING 400 - 601 West Broadway
Vancouver, BC V5Z 4C2
SIGNATURE _____ DATE 99/07/02

NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

This application is a continuation-in-part of copending US Patent Application No. Serial No. 09/030,482, filed February 25, 1998, which is a 111(a) application claiming priority from US Provisional Application No. 60/039,204, filed February 28, 1997, both of which are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to novel mammalian (including human) calcium channel compositions, and to the expression of these compositions in cell lines for use in evaluating calcium channel function and the behavior of compositions which modulate calcium channel function.

BACKGROUND OF THE INVENTION

The rapid entry of calcium into cells is mediated by a class of proteins called voltage-gated calcium channels. Calcium channels are a heterogeneous class of molecules that respond to depolarization by opening a calcium-selective pore through the plasma membrane. The entry of calcium into cells mediates a wide variety of cellular and physiological responses including excitation-contraction coupling, hormone secretion and gene expression. In neurons, calcium entry directly affects membrane potential and contributes to electrical properties such as excitability, repetitive firing patterns and pacemaker activity. Miller, R.J. (1987) "Multiple calcium channels and neuronal function." *Science* 235:46-52. Calcium entry further affects neuronal functions by directly regulating calcium-dependent ion channels and modulating the activity of calcium-dependent enzymes such as protein kinase C and calmodulin-dependent protein kinase II. An increase in calcium concentration at the presynaptic nerve terminal triggers the release of neurotransmitter. Calcium entry also plays a

role in neurite outgrowth and growth cone migration in developing neurons and has been implicated in long-term changes in neuronal activity.

In addition to the variety of normal physiological functions mediated by calcium channels, they are also implicated in a number of human disorders. Recently, mutations identified in human and mouse calcium channel genes have been found to account for several disorders including, familial hemiplegic migraine, episodic ataxia type 2, cerebellar ataxia, absence epilepsy and seizures. Fletcher, et al. (1996) "Absence epilepsy in tottering mutant mice is associated with calcium channel defects." *Cell* 87:607-617; Burgess, et al. (1997) "Mutation of the Ca2+ channel β subunit gene Cchb4 is associated with ataxia and seizures in the lethargic (lh) mouse." *Cell* 88:385-392; Ophoff, et al. (1996) "Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4." *Cell* 87:543-552; Zhuchenko, O. et al. (1997) "Autosomal dominant cerebellar ataxia (SCA6) associated with the small polyglutamine expansions in the α1A-voltage-dependent calcium channel." *Nature Genetics* 15:62-69.

The clinical treatment of some disorders has been aided by the development of therapeutic calcium channel antagonists. Janis, et al. (1991) in *Calcium Channels: Their Properties, Functions, Regulation and Clinical Relevance.* CRC Press, London.

Native calcium channels have been classified by their electrophysiological and pharmacological properties as T, L, N, P and Q types (for reviews see McCleskey, et al. (1991) "Functional properties of voltage-dependent calcium channels." *Curr. Topics Membr.* 39: 295-326, and Dunlap, et al. (1995) "Exocytotic Ca^{2+} channels in mammalian central neurons." *Trends Neurosci.* 18:89-98.). T-type (or low voltage-activated) channels describe a broad class of molecules that activate at negative potentials and are highly sensitive to changes in resting potential. The L, N, P and Q-type channels activate at more positive potentials and display diverse kinetics and voltage-dependent properties. There is some overlap in biophysical properties of the high voltage-activated channels, consequently pharmacological profiles are useful to further distinguish them. L-type channels are sensitive

to dihydropyridine (DHP) agonists and antagonists, N-type channels are blocked by the *Conus geographus* peptide toxin, ω-conotoxin GVIA, and P-type channels are blocked by the peptide ω-agatoxin IVA from the venom of the funnel web spider, *Agelenopsis aperta*. A fourth type of high voltage-activated Ca channel (Q-type) has been described, although whether the Q- and P-type channels are distinct molecular entities is controversial (Sather et al. (1993) "Distinctive biophysical and pharmacological properties of class A (B1) calcium channel α1 subunits." *Neuron* 11: 291-303; Stea, et al. (1994) "Localization and functional properties of a rat brain α1A calcium channel reflect similarities to neuronal Q- and P-type channels." *Proc Natl Acad Sci (USA)* 91: 10576-10580.). Several types of calcium conductances do not fall neatly into any of the above categories and there is variability of properties even within a category suggesting that additional calcium channels subtypes remain to be classified.

Biochemical analyses show that neuronal high-threshold calcium channels are heterooligomeric complexes consisting of three distinct subunits (α_1, $\alpha_2\delta$ and β)(reviewed by De Waard, et al. (1997) in *Ion Channels*, Volume 4, edited by Narahashi, T. Plenum Press, New York). The α_1 subunit is the major pore-forming subunit and contains the voltage sensor and binding sites for calcium channel antagonists. The mainly extracellular α_2 is disulphide-linked to the transmembrane δ subunit and both are derived from the same gene and are proteolytically cleaved *in vivo*. The β subunit is a non-glycosylated, hydrophilic protein with a high affinity of binding to a cytoplasmic region of the α_1 subunit. A fourth subunit, γ, is unique to L-type Ca channels expressed in skeletal muscle T-tubules. The isolation and characterization of γ-subunit-encoding cDNAs is described in US Patent No. 5,386,025 which is incorporated herein by reference.

Molecular cloning has revealed the cDNA and corresponding amino acid sequences of six different types of α_1 subunits (α_{1A}, α_{1B}, α_{1C}, α_{1D}, α_{1E} and α_{1S}) and four types of β subunits (β_1, β_2, β_3 and β_4)(reviewed in Stea, A., Soong, T.W. and Snutch, T.P. (1994) "Voltage-gated calcium channels." in *Handbook of Receptors and Channels*. Edited by R.A. North, CRC

Press.). PCT Patent Publication WO 95/04144, which is incorporated herein by reference, discloses the sequence and expression of α_{1E} calcium channel subunits.

The different classes of α1 and β subunits have been identified in different animals including, rat, rabbit and human and share a significant degree of amino acid conservation across species (for examples see: Castellano, et al. (1993) "Cloning and expression of a third calcium channel β subunit." *J. Biol. Chem.* 268: 3450-3455; Castellano, et al. (1993) "Cloning and expression of a neuronal calcium channel β subunit." *J. Biol. Chem.* 268: 12359-12366; Dubel, et al. (1992). "Molecular cloning of the α_1 subunit of an ω-conotoxin-sensitive calcium channel." *Proc. Natl. Acad. Sci. (USA)* 89: 5058-5062; Fujita, et al.. (1993) "Primary structure and functional expression of the ω-conotoxin-sensitive N-type calcium channel from rabbit brain." *Neuron* 10: 585-598; Mikami, et al.. (1989). "Primary structure and functional expression of the cardiac dihydropyridine-sensitive calcium channel." *Nature* 340: 230-233; Mori, et al. (1991) "Primary structure and functional expression from complementary DNA of a brain calcium channel." *Nature* 350: 398-402; Perez-Reyes, et al. (1992). "Cloning and expression of a cardiac/brain ß subunit of the L-type calcium channel." *J. Biol. Chem.* 267: 1792-1797; Pragnell, et al. (1991). "Cloning and tissue-specific expression of the brain calcium channel β-subunit." *FEBS Lett.* 291: 253-258; Snutch, et al. (1991) "Distinct calcium channels are generated by alternative splicing and are differentially expressed in the mammalian CNS." *Neuron* 7: 45-57; Soong, et al. (1993) "Structure and functional expression of a member of the low voltage-activated calcium channel family." *Science* 260: 1133-1136; Tomlinson, et al. (1993) "Functional properties of a neuronal class C L-type channel." *Neuropharmacology* 32: 1117-1126; Williams, et al. (1992) "Structure and functional expression of α1, α2, and ß subunits of a novel human neuronal calcium channel subtype." *Neuron* 8: 71-84; Williams, et al. (1992) "Structure and functional expression of an ω-conotoxin-sensitive human N-type calcium channel." *Science* 257: 389-395.

In some expression systems the α_1 subunits alone can form functional calcium channels although their electrophysiological and pharmacological properties can be differentially modulated by coexpression with any of the four β subunits. Until recently, the reported modulatory affects of β subunit coexpression were to mainly alter kinetic and voltage-dependent properties. More recently it has been shown that β subunits also play crucial roles in modulating channel activity by protein kinase A, protein kinase C and direct G-protein interaction. (Bourinet, et al. (1994) "Voltage-dependent facilitation of a neuronal α1C L-type calcium channel." *EMBO J.* 13: 5032-5039; Stea, et al. (1995) "Determinants of PKC-dependent modulation of a family of neuronal calcium channels." *Neuron* 15:929-940; Bourinet, et al. (1996) "Determinants of the G-protein-dependent opioid modulation of neuronal calcium channels." *Proc. Natl. Acad. Sci. (USA)* 93: 1486-1491.)

The electrophysiological and pharmacological properties of the calcium channels cloned to date can be summarized as shown in Table 1. While the cloned α_1 subunits identified to date correspond to several of the calcium channels found in cells, they do not account for all types of calcium conductances described in native cells. For example, they do not account for the various properties described for the heterogenous family described as T-type calcium channels. Furthermore, they do not account for novel calcium channels described in cerebellar granule cells or other types of cells. (Forti, et al (1993) "Functional diversity of L-type calcium channels in rat cerebellar neurons." *Neuron* 10: 437-450; Tottene,et al. (1996). "Functional diversity of P-type and R-type calcium channels in rat cerebellar neurons." *J. Neurosci.* 16: 6353-6363).

Because of the importance of calcium channels in cellular metabolism and human disease, it would be desirable to identify the remaining classes of α_1 subunits, and to develop expression systems for these subunits which would permit the study and characterization of these calcium channels, including the study of pharmacological modulators of calcium channel function. Thus, it is an object of the present invention to provide heretofor undisclosed calcium channels having novel α_1 subunits, including cell lines expressing these

TABLE 1

	ω-conotoxin GVIA	1,4-dihydropyridines	cadmium	ω-agatoxin IVA	ω-conotoxin MVIIC	native Ca^{2+} channel type
α_{1A}	-	-	✓	✓	✓	P/Q-type
α_{1B}	✓	-	✓	-	✓	N-type
α_{1C}	-	✓	✓	-	-	L-type
α_{1D}	-	✓	✓	-	-	L-type
α_{1E}	-	-	✓	-	-	novel
α_{1S}	-	✓	✓	-	-	L-type

new calcium channels. It is a further object of the present invention to provide a method for testing these novel calcium channels using such cell lines.

SUMMARY OF THE INVENTION

The present invention provides sequences for a novel mammalian calcium channel subunits of T-type calcium channels, which we have labeled as α_{1G}, α_{1H} and α_{1I} subunits. Knowledge of the sequences of these calcium channel subunits may be used in the development of probes for mapping the distribution and expression of the subunits in target tissues. In addition, these subunits, either alone or assembled with other proteins, can produce functional calcium channels, which can be evaluated in model cell lines to determine the properties of the channels containing the subunits of the invention. These cell lines can be used to evaluates the affects of pharmaceuticals and/or toxic substances on calcium channels incorporating α_{1G}, α_{1H} and α_{1I} subunits

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A and B show a comparison of the waveforms and current voltage relationship for α_{1G};

Figs. 2A and Bshow a comparison of the waveforms and current voltage relationship for α_{1I} calcium channels.

Fig. 3 shows a comparison of the steady state inactivation profiles of the α_{1G} and α_{1I} calcium channels.

Figs. 4A-C show a comparison of the inactivation kinetics of the α_{1G} and α_{1I} calcium channels.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes the following aspects for which protection is sought:

(a) novel mammalian (including human) calcium channel subunits and DNA sequences encoding such subunits. Specifically, the invention encompasses an at least partially purified DNA molecule comprising a sequence of nucleotides that encodes an α subunit of a T-type calcium channel, and such α subunits *per se*. It will be appreciated that polymorphic variations may be made or may exist in the DNA of some individuals leading to minor deviations in the DNA or amino acids sequences from those shown which do not lead to any substantial alteration in the function of the calcium channel. Such variations, including variations which lead to substitutions of amino acids having similar properties are considered to be within the scope of the present invention. Thus, in one embodiment, the present application claims DNA molecules which encode α_1 subunits of mammalian T-type calcium channels, and which hybridize under conditions of medium (or higher) hybridization stringency with one or another of the specific sequences disclosed in this application. This level of hybridization stringency is generally sufficient given the length of the seqeunces involved to permit recovery of the subunits within the scope of the invention from mammalian DNA libraries.

(b) polynucleotide sequences useful as probes in screening human cDNA libraries for genes encoding these novel calcium channel subunits. These probes can also be used in histological assay to determine the tissue distribution of the novel calcium channel subunits.

(c) at least partially purified α_1 subunits and related peptides for mammalian T-type calcium channels. These proteins and peptides can be used to generate polyclonal or monoclonal antibodies to determine the cellular and subcellular distribution of T-type calcium channel subunits.

(d) eukaryotic cell lines expressing the novel calcium channel subunits. These cell lines can be used to evaluate compounds as pharmacological modifiers of the function of the novel calcium channel subunits.

(e) a method for evaluating compounds as pharmacological modifiers of the function of the novel calcium channel subunits using the cell lines expressing those subunits alone or in combination with other calcium channel subunits.

Further, since defects in the novel calcium channel subunits may be associated with a human genetic disease including, but not limited to; epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome and Parkinson's disease; characterization of such associations and ultimately diagnosis of associated diseases can be carried out with probes which bind to the wild-type or defective forms of the novel calcium channels.

As used in the specification and claims of this application, the term "T-type calcium channel" refers to a voltage-gated calcium channel having a low activation voltage, generally less than -50 mV, and most commonly less than -60 mV. T-type calcium channels also exhibit comparatively negative steady-state inactivation properties and slow deactivation kinetics. The terms "α_1 subunit" or "α_1 calcium channel" refer to a protein subunit of a calcium channel which is responsible for pore formation and contains the voltage sensor and binding sites for calcium channel agonists and antagonists. Such subunits may be independently functional as calcium channels or may require the presence of other subunit types for complete functionality.

As used in the specification and claims of this application, the phrase "at least partially purified" refers to DNA or protein preparations in the which the specified molecule has been separated from adjacent cellular components and molecules with which it occurs in the natural state, either by virtue of performing a physical separation process or by virtue of making the DNA or protein molecule in a non-natural environment in the first place. The term encompasses cDNA molecules and expression vectors.

In accordance with the present invention, we have identified mammalian DNA sequences which code for novel T-type calcium channel α_1 subunits. These subunits are

believed to represent new types of α_1 subunits of mammalian voltage-dependent calcium channels which have been designated as types α_{1G}, α_{1H} and α_{1I}.

The novel α_1 subunits of the invention were identified by screening the *C. elegans* genomic DNA sequence data base for sequences homologous to previously identified mammalian calcium channel α_1 subunits. Specifically, the following twelve mammalian α_1 subunit sequences were used to screen the *C. elegans* genomic data bank:

rat brain α_{1A} : GTCAAAACTC AGGCCTTCTA CTGG	SEQ ID. No. 1
rat brain α_{1A} : AACGTGTTCT TGGCTATCGC GGTG	SEQ ID. No. 2
rat brain α_{1B} : GTGAAAGCAC AGAGCTTCTA CTGG	SEQ ID. No. 3
rat brain α_{1B} : AACGTTTTCT TGGCCATTGC TGTG	SEQ ID. No. 4
rat brain α_{1C} : GTTAAATCCA ACGTCTTCTA CTGG	SEQ ID. No. 5
rat brain α_{1C} : AATGTGTTCT TGGCCATTGC GGTG	SEQ ID. No. 6
rat brain α_{1D} : GTGAAGTCTG TCACGTTTTA CTGG	SEQ ID. No. 7
rat brain α_{1D} : AAGCTCTTCT TGGCCATTGC TGTA	SEQ ID. No. 8
rat brain α_{1E} : GTCAAGTCGC AAGTGTTCTA CTGG	SEQ ID. No. 9
rat brain α_{1E} : AATGTATTCT TGGCTATCGC TGTG	SEQ ID. No. 10
rat brain consensus #1 : ATCTAYGCYR TSATYGGSAT G	SEQ ID. No. 11
rat brain consensus #2 : ATGGACAAYT TYGASTAYTC	SEQ ID. No. 12

This search identified four distinct *C. elegans* cosmids that contain open reading frames (coding regions) that exhibit homology to mammalian calcium channel α_1 subunits:

cosmid and reading frame T02C5.5

cosmid and reading frame C48A7.1

cosmid and reading frame C54D2.5

cosmid and reading frame C27F2.3

Examination of the four *C. elegans* cosmid sequences by phylogeny analysis shows that two of these, T02C5.5 and C48A7.1, correspond closely with previously identified mammalian α_1 subunits. T02C5.5 appears to be an ancestral member related to the mammalian α_{1A}, α_{1B} and α_{1E} subunits. C48A7.1 appears to be an ancestral member related to the mammalian L-type channels encoded by α_{1C}, α_{1D} and α_{1S}. In contrast, the *C. elegans* cosmids C54D2.5 and C27F2.3 identify novel types of calcium channel α_1 subunits distinct from the other mammalian subtypes.

Mammalian counterparts of the *C. elegans* calcium channel α_1 subunit encoded by C54D2.5 were identified by screening of the GenBank expressed sequence tag (EST) data bank. This analysis identified a total of 13 mammalian sequences that exhibit some degree of DNA sequence and amino acid identity to C54D2.5, of which 8 are human sequences. (Table 2) Some of these sequences appear unlikely to encode novel calcium channel subunits because they either exhibit a significant degree of homology to previously identified mammalian α_1 subunits (for example, clones H06096 and H14053) or exhibit homology in a region not considered to be diagnostic of calcium channel α_1 subunits specifically as opposed to other types of ion channel molecules in general (for example, clone D20469). One of the five remaining sequences was evaluated and appears to encode a sodium channel. Four sequences (H55225, H55617, H55223, and H55544), however, encode what are believed to be previously unidentified calcium channel α_1 subunits. For these subunits, the amino acid sequences closely match that of known calcium channel subunits in conserved regions but are sufficiently different to indicate that they do not encode previously identified mammalian calcium channel α_1 subunits, α_{1A}, α_{1B}, α_{1C}, α_{1D}, α_{1E}, or α_{1S}. The expected amino acid sequence closely matches but is not identical to amino acid sequences in these known calcium channel subunits.

Table 2

Query = C54D2.5 CE02562 CALCIUM CHANNEL ALPHA-1 SUBUNIT LG:6

Database: Non-redundant Database of GenBank EST Division
824,500 sequences; 302,742,428 total letter

Sequences producing High-scoring Segment Pairs:		Frame	Score	P(N)
gb|AA183990|AA183990	ms53e02.r1 Life Tech mouse embry...	+1	108	1.8e-24
gb|H55225|H55225	**CHR220164 Homo sapiens genomic c...**	**+1**	**136**	**2.5e-10**
dbj|D68412|CELK131B1F	C.elegans cDNA clone yk131b1 : 5...	+3	117	1.7e-06
gb|R75128|R75128	MDB1075 Mouse brain, Stratagene ...	+3	113	7.2e-06
gb|H55617|H55617	**CHR220556 Homo sapiens genomic c...**	**+2**	**102**	**2.8e-05**
emb|F07776|HSC2HD061	**H. sapiens partial cDNA sequence...**	**+3**	**100**	**0.00057**
gb|W76774|W76774	me84e08.r1 Soares mouse embryo N...	+2	98	0.0012
gb|H06096|H06096	yl77e01.r1 Homo sapiens cDNA clo...	+3	98	0.0015
gb|H14053|H14053	ym65d10.r1 Homo sapiens cDNA clo...	+2	91	0.0036
gb|H55223|H55223	**CHR220162 Homo sapiens genomic c...**	**+2**	**87**	**0.0039**
dbj|D35703|CELK024D9F	C.elegans cDNA clone yk24d9 : 5'...	+3	74	0.046
dbj|D20469|HUMGS01443	Human HL60 3'directed MboI cDNA,...	-2	66	0.91
gb|H55544|H55544	**CHR220483 Homo sapiens genomic c...**	**+1**	**65**	**0.98**

The four sequences (H55225, H55617, H55223, and H55544) are found on human chromosome 22, and are now believed to all be part of the same gene encoding the novel human calcium channel subunit α_{1I}.

The sequences of the four selected sequences and the references from which they are taken are given as follows:

H55225 SOURCE human clone=C22_207 primer=T3 library=Chromosome 22 exon

Trofatter, et al., *Genome Res.* 5 (3): 214-224 (1995)

SEQ ID No. 13

1 GTGATCACTC TGGAAGGCTG GGTGGAGATC ATGTACTACG TGATGGATGC TCACTCCTTC

61 TACAACTTCA TCTACTTCAT CCTGCTTATC ATACCCCTCT TGCCTTGCAC CCCATATGGT

121 CTTCCCAGAG TGAGCTCATC CACCTCGTCA TGCCTGACTC GACGTTCA

H55617 SOURCE human clone=C22_757 primer=T3 library=Chromosome 22 exon

Trofatter, et al., *Genome Res.* 5 (3): 214-224 (1995)

SEQ ID No. 14

1 GATGGTCGAG TACTCCCTGG ACCTTCAGAA CATCAACCTG TCAGCCATCC GCACCGTGCG

61 CGTCCTGAGG CCCCTCAAAG CCATCAACCG CGTGCCCA

H55223 SOURCE human clone=C22_204 primer=T3 library=Chromosome 22 exon

Trofatter, et al, *Genome Res.* 5 (3): 214-224 (1995)

SEQ ID No. 15

1 CATGCTGGTG ATCCTGCTGA ACTGCGTGAC ACTTGGCATG TACCAGCCGT GCGACGACAT

61 GGACTGCCTG TCCGACCGCT GCAAGATCCT GCAG

H55544 SOURCE human clone=C22_651 primer=T3 library=Chromosome 22 exon

Trofatter, et al, *Genome Res.* 5 (3): 214-224 (1995)

SEQ ID No. 16

1 GTATCTCTGG TTACTTTAGT AGCCAACACT CTTGGCTACT CAGACCTTGG TCCCATTAAA

61 TCCCTGCGAA CCTTGAGAGC ACTAAGACCT CTAAGAGCTT TGTCTAGATT TGAAGGAATG

121 AGG

A search of the Sanger Genome Sequencing Center (Cambridge, U.K.) and the Washington University Genome Sequencing Center (St. Louis. MO) sequences in progress revealed a Bacterial Artificial Chromosome (BAC) sequence (bK206c7) that contained matches to the *C. elegans* cosmid open reading frame, C54D2.5, and to the four human

chromosome 22 ESTs, H55225, H55617, H55223,H55544. The C. elegans C54D2.5 cosmid sequence and the human EST sequences were then used to compare the translation of the bK206c7 BAC genomic sequence in all 6 reading frames. The analysis was performed using the graphical program Dotter (Eric Sohnhammer, NCBI). The analysis revealed a series of potential coding regions on one strand of the bK206c7 BAC sequence. These were subsequently translated in all 3 reading frames and the potential splice junctions identified. The translated sequence of this longer DNA fragment which is part of the human α_{II} subunit gene is given by Seq. ID Nos. 17 and 18.

Using the sequence information from the four EST's, a full length gene can be recovered using any of several techniques. Polynucleotide probes having a sequence which corresponds to or hybridizes with the EST sequences or a distinctive portion thereof (for example oligonucleotide probes having a length of 18 to 100 nucleotides) can be used to probe a human cDNA library for identification of the full length DNA encoding the α_{II} subunits. The process of identifying cDNAs of interest using defined probes is well known in the art and is, for example, described in International Patent Publication No. WO95/04144, which is incorporated herein by reference. This process generally involves screening bacterial hosts (e.g. *E. coli*) harboring the library plasmids or infected with recombinant lambda phage with labeled probes, e.g. radiolabeled with ^{32}P, and selection of colonies or phage which bind the labeled probe. Each selected colony or phage is grown up, and the plasmids are recovered. Human cDNAs are recovered from the plasmids by restriction digestion, or can be amplified, for example by PCR. The recovered cDNA can be sequenced, and the position of the calcium channel subunit-encoding region further refined, although neither process is not necessary to the further use of the cDNA to produce cell lines expressing the novel calcium channel subunits.

Longer portions of DNA-encoding the novel calcium channel subunits of the invention can also be recovered by PCR cloning techniques using primers corresponding to or based upon the EST sequences. Using this technique to identify relevant sequences within a human

brain total RNA preparation confirmed that the novel α_{1I} calcium channel subunit is present in human brain. Subcloning of the 567 nt PCR product (Seq. ID No. 19, amino acids Seq. ID No. 20) and subsequent sequencing thereof showed that this product corresponds to the derived sequence form the bK206c7 BAC genomic sequence, the nucleotide sequence of which is given as SEQ ID No. 17 (amino acid sequence Seq. ID No. 18). The same experiment was performed using a rat brain RNA preparation and resulted in recovery of a substantially identical PCR product. (SEQ ID. No. 21). The protein encoded by the rat PCR product (SEQ ID No. 22) is 96% identical to the human PCR product (Seq. ID No. 20).

These sequences, which encode a partial subunit can be used as a basis for constructing full length human or rat α_{1I} clones. Briefly, the subcloned α_{1I} PCR product is radiolabeled by random hexamer priming according to standard methods (See, Sambrook , J., Fritsch, E.F. and Maniatis, T. (1989) *Molecular Cloning, A Laboratory Manual.* Cold Spring Harbor Press) and used to screen commercial human brain cDNA libraries (Stratagene, La Jolla, CA). The screening of cDNA libraries follows standard methods and includes such protocols as infecting bacteria with recombinant lambda phage, immobilizing lambda DNA to nitrocellulose filters and screening under medium hybridization stringency conditions with radiolabeled probe. cDNA clones homologous to the probe are identified by autoradiography. Positive clones are purified by sequential rounds of screening.

Following this protocol, most purified cDNA's are likely to be partial sequence clones due the nature of the cDNA library synthesis. Full length clones are constructed from cDNA's which overlap in DNA sequence. Restriction enzyme sites which overlap between cDNAs are used to ligate the individual cDNA's to generate a full-length cDNA. For subsequent heterologous expression, the full-length cDNA is subcloned directly into an appropriate vertebrate expression vector, such as pcDNA-3 (Invitrogen, San Diego, CA) in which expression of the cDNA is under the control of a promoter such as the CMV major intermediate early promoter/enhancer. Other suitable expression vectors include, for example, pMT2, pRC/CMV, pcDNA3.1 and pCEP4.

Following these protocols, as described more fully in Example 4, full length mammalian α_{1G}, α_{1H} and α_{1I} calcium channel subunit cDNAs were isolated by using the 567 base pair human fragment (Seq. ID No. 19) to screen a rat brain cDNA library. Sequencing of the recovered sequences identified the three distinct classes of calcium channel subunits which have been demoninated herein as α_{1G}, α_{1H} and α_{1I} subunits. For each class of subunit, complete sequencing of the largest cDNA confirmed that it represented only a portion of the predicted calcium channel coding region. Complete sequences for the three new subunits were obtained by rescreening the rat brain cDNA library with probes derived from the partial length cDNAs to obtain overlapping segments. These segments were combined to form a complete gene by restriction digestion and ligation. The complete cDNA sequences of the rat α_{1G}, α_{1H} and α_{1I} subunits are given by Sequence ID Nos. 23, 25 and 27, respectively. Corresponding amino acid sequences are given by Sequence ID Nos. 24, 26 and 28. The same techniques are employed to recover human sequences by screening of a human or other mammalian library. Thus, for example, partial length human sequences for α_{1G} and α_{1H} T-type calcium channels have been recovered using the same probe (Seq. ID No. 19) and the full length rat α_{1I} cDNA (Seq. ID. No. 27) has been used to recover a partial length DNA encoding a human α_{1I} T-type calcium channel. The DNA and amino acid sequences for these partial length human calcium channels are given by Seq. ID Nos. 30-35.

Once the full length cDNA is cloned into an expression vector, the vector is then transfected into a host cell for expression. Suitable host cells include *Xenopus* oocytes or mammalian cells such as human embryonic kidney cells as described in International Patent Publication No. WO 96/39512 which is incorporated herein by reference and Ltk cells as described in US Patent No. 5,386,025 which is incorporated herein by reference. Transfection into host cells may be accomplished by microinjection, lipofection, glycerol shock, electroporation calcium phosphate or particle-mediated gene transfer. The vector may also be transfected into host cells to provide coexpression of the novel α_1 subunits with a β and/or an $\alpha_2\delta$ subunit.

To confirm that the three full length cDNAs (sequence ID Nos. 23, 25 and 27) encoded function calcium channels, the α_{1G} and α_{1I} cDNAs were transiently transfected into human embryonic kidney cells and evaluated using electrophysiological recording techniques. As described in more detail in Example 5 below, and as illustrated in Figs. 1-4), the results are consistent with a role of these subunits in native T-type channels in nerve, muscle and endocrine cells.

The resulting cell lines expressing functional calcium channels including the novel α_1 subunits of the invention can be used test compounds for pharmacological activity with respect to these calcium channels. Thus, the cell lines are useful for screening compounds for pharmaceutical utility. Such screening can be carried out using several available methods for evaluation of the interaction, if any, between the test compound and the calcium channel. One such method involves the binding of radiolabeled agents that interact with the calcium channel and subsequent analysis of equilibrium binding measurements including but not limited to, on rates, off rates, K_d values and competitive binding by other molecules. Another such method involves the screening for the effects of compounds by electrophysiological assay whereby individual cells are impaled with a microelectrode and currents through the calcium channel are recorded before and after application of the compound of interest. Another method, high-throughput spectrophotometric assay, utilizes the loading the cell lines with a fluorescent dye sensitive to intracellular calcium concentration and subsequent examination of the effects of compounds on the ability of depolarization by potassium chloride or other means to alter intracellular calcium levels. Compounds to be tested as agonists or antagonists of the novel α_{1I} calcium channel subunits are combined with cells that are stably or transiently transformed with a DNA sequence encoding the α_{1G}, α_{1H} and α_{1I} calcium channel subunits of the invention and monitored using one of these techniques.

DNA fragments with sequences given by SEQ ID Nos. 13-17 and 19, or polynucleotides with the complete coding sequences as given by Sequence ID Nos. 23, 25 and 27 or distinctive portions thereof which do not exhibit non-discriminatory levels of homology

with other types of calcium channel subunits may also be used for mapping the distribution of α_{1G}, α_{1H} and α_{1I} calcium channel subunits within a tissue sample. This method follows normal histological procedures using a nucleic acid probe, and generally involves the steps of exposing the tissue to a reagent comprising a directly or indirectly detectable label coupled to a selected DNA fragment, and detecting reagent that has bound to the tissue. Suitable labels include fluorescent labels, enzyme labels, chromophores and radio-labels.

EXAMPLE 1

In order to isolate novel human calcium channel α_1 subunits using standard molecular cloning protocols, synthetic DNA probes are prepared, radiolabeled with ^{32}P and utilized to screen human cDNA libraries commercially available in lambda phage vectors (Stratagene, La Jolla, CA) based on the human DNA sequences for H55225, H55617, H55223, and H55544. DNA fragments with the sequence of sequence ID Nos 17 and 19 may also be used for this purpose. Positive phage are purified through several rounds of screening involving immobilizing the phage DNA on nitrocellulose filters, hybridizing with the radiolabeled probe, washing off of excess probe and then selection of clones by autoradiography. Clones identified by this approach are expected to be partial length clones due to the nature of cDNA library synthesis and several rounds of screening for each calcium channel type may be necessary to obtain full-length clones.

To characterize the clones, double stranded plasmid DNA is prepared from the identified clones and the sequences are determined using ^{35}S dATP, Sequenase and standard gel electrophoresis methods. Regions of similarity and regions of overlap are determined by comparison of each cDNA sequence.

Full-length clones are constructed by ligating overlapping cDNA fragments together at common restriction enzyme sites. The full-length clones are subsequently inserted into vectors suitable for expression in vertebrate cells (e.g. pMT2, pRC/CMV, pcDNA3.1, pCEP4,

pREP7) by ligation into restriction sites in the vector polylinker region which is downstream of the promoter used to direct cDNA expression.

DNA encoding the novel calcium channels can be stably or transiently introduced into eukaryotic cells (e.g. human embryonic kidney, mouse L cells, chinese hamster ovary, etc) by any number of available standard methods. Stable transfection is achieved by growing the cells under conditions that promote growth of cells expressing a marker gene which is contained in the expression vector (e.g. dihydrofolate reductase, `thymidine kinase, or the like). The heterologous DNA encoding the human calcium channel may be integrated into the genome or may be maintained as an episomal element.

Expression of the human calcium channel in transfected cells may monitored by any number of techniques, including Northern blot for RNA analysis, Southern blot for cDNA detection, electrophysiological assay for calcium channel function, the binding of radiolabeled agents thought to interact with the calcium channel, and fluorescent assay of dyes sensitive to intracellular calcium concentration.

EXAMPLE 2

Heterologous Expression of Mammalian α_{1I} Calcium Channels in Cells

A. Transient Transfection in Mammalian Cells

Host cells, such as human embryonic kidney cells, HEK 293 (ATCC# CRL 1573) are grown in standard DMEM medium supplemented with 2 mM glutamine and 10% fetal bovine serum. HEK 293 cells are transfected by a standard calcium-phosphate-DNA co-precipitation method using a full-length mammalian α_{1I} calcium channel cDNA (for example, Seq. ID. No. 27) in a vertebrate expression vector (for example see Current protocols in Molecular Biology). The α_{1I} calcium channel cDNA may be transfected alone or in combination with other cloned subunits for mammalian calcium channels, such as $\alpha 2\delta$ and β subunits, and also with clones for marker proteins such the jellyfish green fluorescent protein.

Electrophysiological Recording: After an incubation period of from 24 to 72 hrs the culture medium is removed and replaced with external recording solution (see below). Whole cell patch clamp experiments are performed using an Axopatch 200B amplifier (Axon Instruments, Burlingame, CA) linked to an IBM compatible personal computer equipped with pCLAMP software. Microelectrodes are filled with 3 M CsCl and have typical resistances from 0.5 to 2.5 MΩ. The external recording solution is 20 mM $BaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 40 mM TEACl, 10 mM Glucose, 65 mM CsCl, (pH 7.2). The internal pipette solution is 105 mM CsCl, 25 mM TEACl, 1 mM $CaCl_2$, 11 mM EGTA, 10 mM HEPES (pH 7.2). Currents are typically elicited from a holding potential of -100 mV to various test potentials. Data are filtered at 1 kHz and recorded directly on the harddrive of a personal computer. Leak subtraction is carried out on-line using a standard P/5 protocol. Currents are analyzed using pCLAMP versions 5.5 and 6.0. Macroscopic current-voltage relations are fitted with the equation $I = \{1/(1+\exp(-(V_m-V_h)/S)\} \times G - (V_m-E_{rev})$, where V_m is the test potential, V_h is the voltage at which half of the channels are activated, and S reflects the steepness of the activation curve and is an indication of the effective gating charge movement. Inactivation curves are normalized to 1 and fitted with $I = (1/1 + \exp((V_m-V_h)/S)$ with V_m being the holding potential. Single channel recordings are performed in the cell-attached mode with the following pipette solution (in mM): 100 $BaCl_2$, 10 HEPES, pH 7.4 and bath solution: 100 KCl, 10 EGTA, 2 $MgCl_2$, 10 HEPES, pH 7.4.

B. Transient Transfection in Xenopus Oocytes

Stage V and VI Xenopus oocytes are prepared as described by Dascal et al (1986), Expression and modulation of voltage-gated calcium channels after RNA injection into Xenopus oocytes. Science 231:1147-1150. After enzymatic dissociation with collagenase, oocytes nuclei are microinjected with the human α_{1I} calcium channel cDNA expression vector construct (approximately 10 ng DNA per nucleus) using a Drummond nanoject apparatus. The α_{1I} calcium channel may be injected alone, or in combination with other mammalian

calcium channel subunit cDNAs, such as the α2-δ and β1b subunits. After incubation from 48 to 96 hrs macroscopic currents are recorded using a standard two microelectrode voltage-clamp (Axoclamp 2A, Axon Instruments, Burlingame, CA) in a bathing medium containing (in mM): 40 $Ba(OH)_2$, 25 TEA-OH, 25 NaOH, 2 CsOH, 5 HEPES (pH titrated to 7.3 with methan-sulfonic acid). Pipettes of typical resistance ranging from 0.5 to 1.5 mΩ are filled with 2.8M CsCl, 0.2M CsOH, 10mM HEPES, 10mM BAPTA free acid. Endogenous Ca (and Ba) -activated Cl currents are suppressed by systematically injecting 10-30 nl of a solution containing 100mM BAPTA-free acid, 10mM HEPES (pH titrated to 7.2 with CsOH) using a third pipette connected to a pneumatic injector. Leak currents and capacitive transients are subtracted using a standard P/5 procedure.

EXAMPLE 3

Construction of Stable Cell Lines Expressing Mammalian α_{1I} Calcium Channels

Mammalian cell lines stably expressing human α_{1I} calcium channels are constructed by transfecting the α_{1I} calcium channel cDNA into mammalian cells such as HEK 293 and selecting for antibiotic resistance encoded for by an expression vector. Briefly, a full-length mammalian α_{1I} calcium channel cDNA (for example Seq. ID No. 27) subcloned into a vertebrate expression vector with a selectable marker, such as the pcDNA3 (InvitroGen, San Diego, CA), is transfected into HEK 293 cells by calcium phosphate coprecipitation or lipofection or electroporation or other method according to well known procedures (Methods in Enzymology, Volume 185, Gene Expression Technology (1990) Edited by Goeddel, D.V.). The α_{1I} calcium channel may be transfected alone, or in combination with other mammalian calcium channel subunit cDNAs, such as the α2-δ and β1b subunits, either in a similar expression vector or other type of vector using different selectable markers. After incubation for 2 days in nonselective conditions, the medium is supplemented with Geneticin (G418) at a concentration of between 600 to 800 ug/ml. After 3 to 4 weeks in this medium, cells which are resistant to G418 are visible and can be cloned as isolated colonies using standard cloning

rings. After growing up each isolated colony to confluency to establish cell lines, the expression of α_{1I} calcium channels can be determined at with standard gene expression methods such as Northern blotting, RNase protection and reverse-transcriptase PCR.

The functional detection of α_{1I} calcium channels in stably transfected cells can be examined electrophysiologically, such as by whole patch clamp or single channel analysis (see above). Other means of detecting functional calcium channels include the use of radiolabeled ^{45}Ca uptake, fluorescence spectroscopy using calcium sensitive dyes such as FURA-2, and the binding or displacement of radiolabeled ligands that interact with the calcium channel.

EXAMPLE 4

In order to recover full-length mammalian sequences for novel calcium channels, the 567 base pair partial length human brain α_{1I} cDNA was gel-purified, radio-labelled with ^{32}P dATP and dCTP by random priming (Feinberg et al., 1983, *Anal. Biochem.* 132: 6-13) and used to screen a rat brain cDNA library constructed in the phase vector Lambda Zapp II. (Snutch et al., 1990, *Proc Natl Acad Sci (USA)* 87: 3391-3395). Screening was carried out at 62°C in 5XSSPE (1XSSPE= 0.18 M NaCl; 1mM EDTA; 10 mM sodium phosphate, pH=7.4 0.3% SDS, 0.2 mg/ml denatured salmon sperm DNA). Filters were washed at 62°C in 0.2X SSPE/0.1% SDS. After three rounds of screening and plaque purification, positive phages were transformed into Bluescript phagemids (Stratagene, La Jolla, CA) by *in vivo* excision.

Double stranded DNA sequencing on the recombinant phagemids was performed using a modified dideoxynucleotide protocol (Biggin et al., 1983, *Proc Natl Acad Sci (USA)* 80:3963-3965) and Sequenase version 2.1 (United States Biochemical Corp.). DNA sequencing identified three distinct classes of calcium channel α_1 subunits: designated as α_{1G}, α_{1H} and α_{1I} calcium channel subunits.

For each class of calcium channel α_1 subunit, the largest cDNA was completely sequenced and determined to represent only a portion of the predicted calcium channnel

coding region. In order to isolate the remaining portions of α_{1G} and α_{1I} calcium channel subunits, the α_{1G} clone was digested with HindIII and SpeI. The resulting 540 base pair fragment was gel purified, radiolabeled with ^{32}P dATP and dCTP by random priming and used to rescreen the rat brain cDNA library as described above. The sequence of the 540 base pair α_{1G} screening probe used is given by Seq. ID No. 29. Other sequences spanning regions of distinctiveness within the sequences for the subunits could also be employed.

Double-stranded DNA sequencing of the purified recombinant phagemids showed that additional α_{1G}, α_{1H} and α_{1I} calcium channel subunit cDNAs overlapped with the original partial length cDNAs and together encoded complete protein coding regions as well as portions of their respective 5' and 3' non-coding untranslated regions.

To recover further human sequences for the novel α_{1G} and α_{1H} calcium channels, the 567 base pair partial length human brain α_{1I} cDNA (Seq. 19) was radio-labelled with ^{32}P dATP and dCTP by random priming and used to screen a commercial human thalamus cDNA library (Clontech). Hybridization was performed overnight at 65 °C in 6 X SSPE; 0.3% SDS; 5X Denhardt's. Filters were washed at 65 °C in 0.1 X SSPE/ 0.3% SDS. After four rounds of screening and plaque purification, positive phages were selected, DNA prepared and the insert cDNA excised form the lambda vector by digestion with Eco R1 restriction enzyme. The excised cDNA was subcloned into the plasmid Bluescript KS (Stratagene, La Jolla, CA) and the DNA sequence determined using a modified dideoxynucleotide protocol and Sequenase version 2.1. The partial length α_{1G} cDNA isolated consisted of 2212 base pairs of which 279 base pairs were 5' noncoding and 1,933 base pairs were coding region representing 644 amino acids (Seq. ID Nos. 30, 31). The partial α_{1H} cDNA isolated consisted of 1,608 base pairs of which 53 base pairs were 5' noncoding and 1,555 were coding region representing 518 amino acids (Seq. ID Nos. 32, 33).

To recover further human sequences for the novel α_{1I} calcium channel, the full-length rat brain α1I cDNA (Seq. 27) was radio-labelled ^{32}P dATP and dCTP by random priming and used to screen a commercial human hippocampus cDNA library (Stratagene). Hybridization

was performed overnight at 65 °C in 6 X SSPE; 0.3% SDS; 5X Denhardt's. Filters were washed at 65 °C in 0.1 X SSPE/ 0.3% SDS. After four rounds of screening and plaque purification, positive phages were transformed into Bluescript phagemids (Stratagene, LA Jolla, CA) by *in vitro* excision. The excised cDNA DNA sequence was determined using a modified dideoxynucleotide protocol and Sequenase version 2.1. The partial α_{1I} cDNA isolated consisted of 1,080 base pairs of coding region representing 360 amino acids (Seq. ID Nos. 34, 35).

EXAMPLE 5

Double-stranded DNA sequencing of the purified recombinant phagemids showed that additional α_{1G} and α_{1I} calcium channel cDNAs overlapped with the original partial length cDNAs and together encoded complete protein coding regions as well as portions of their respective 5' and 3' non-coding untranslated regions. (Seq. ID Nos. 23 and 27, respectively) In addition to the α_{1G} and α_{1I} calcium channel classes, DNA sequencing of the recombinant phagemids also identified a third class of calcium channel α_1 subunit: designated as the α_{1H} calcium channel subunit. The partial length α_{1H} calcium channel cDNAs overlapped and together encoded a complete α_{1H} coding region as well as portions of the 5' and 3' untranslated regions (Seq. ID. No. 25).

Electrophysiological studies were performed on transiently-transfected human embryonic kidney cells (HEK-tsa201) prepared using the general protocol of Example 2. Transfection was carried out by standard calcium phosphate precipitation. (Okayama et al., 1991, *Methods in Molec. Biol.*, Vol. 7, ed. Murray, E.J.). For maintenance, HEK-tsa201 cells were cultured until approximately 70% confluent, the media removed and cells dispersed with trypsin and gentle trituration. Cells were then diluted 1:10 in culture medium (10% FBS, DMEM plus L-glutamine, pen-strp) warmed to 37°C and plated onto tissue culture dishes. For transient transfection, 0.5 mM $CaCl_2$ was mixed with a total of 20 μg of DNA (consisting of 3μg of either rat brain α_{1G} or α_{1I} calcium channel cDNA, 2 μg of CD8 plasmid marker, and

15 μg of Bluescript plasmid carrier DNA). The DNA mixture was mixed thoroughly and then slowly added dropwise to 0.5 ml of 2 times HeBS (274 mM NaCl, 20mM D-glucose, 10mM KCl, 1.4 mM Na_2HPO_4, 40 mM Hepes (pH=7.05). After incubation at room temperature for 20 min, 100 μl of the DNA mixture was slowly added to each dish of HEK-tsa201 cells and then incubated at 37°C for 24 to 48 hours in a tissue culture incubator (5% CO_2).

Positive transfectant cells were identified visually by addition of 1 μl of mouse CD8 (Lyt2) Dynabeads directly to the recording solution and gentle swirling to mix. Whole cell patch clamp readings were carried out with an Axopatch 200A amplifier (Axon Instruments) as described previously. (Zamponi et al., 1997, *Nature* 385: 442-446). The external recording solution was 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 40 mM TEA-Cl, 10 mM glucose, 92 mM CsCl, pH=7.2 with TEA-hydroxide. The internal pipette solutions was 105 mM CsCl, 25 mM TEA-Cl, 1mM $CaCl_2$, 11 mM EGTA, 10 mM HEPES, pH 7.2 with NaOH.

For determination of current-voltage (I-V) relationships, cells were held at a resting potential of -100 mV and then stepped to various depolarizing test potentials. For steady-state inactivation, cells were held at varius potentials for 20 sec. and currents recorded during a subsequent test pulse to the peak potential of the I-V. Leak currents and capacitative transients were subtracted using a P/5 procedure.

Figs. 1-4 show the results obtained for HEK cells transfected with and expressing the cDNA of sequences ID Nos. 23 and 27, which correspond to the subunits designated as α_{1G} and α_{1I}. Figs. 1A and B and 2A and B shows a comparison of the waveforms and current-voltage relationship for the two channel subunit types. In the presence of recording solution containing 2mM Ca^{2+}, both the α_{1G} and α_{1I} channel subunits exhibit activation properties consistent with native T-type calcium currents. Figs 1 A and 2A show the subunit calcium current from a cell held at -120 mV and depolarized to a series of test potentials. Figs 1B and 2B show the magnitude of the calcium current. From a holding potential of -110 mV, both channel first activate at approximately -70 mV and peak currents are obtained between -40 and -50 mV. Upon depolarization to various test potentials, the current waveforms of the α_{1G}

and α_{1I} calcium channels exhibit an overlapping pattern characteristic of native T-type channels in nerve, muscle and endocrine cells.

Fig. 3 shows steady-state inactivation profiles for the α_{1G} and α_{1I} calcium channels in HEK 293 cells transiently transformed with full length cDNAs (SEQ ID Nos 23 or 27) for α_{1G} or α_{1I} subunits. Steady state inactivation properties were determined by stepping from -120 mV to prepulse holding potentials between -120 mV and -50 mV for 15 sec.. prior to a test potential of -30 mV. The data are plotted as nnormalized whole cell current versus prepulse holding potential and show that α_{1G} exhibits a V_{50} of approximately -85 mV and α_{1I} a V_{50} of approximately -93 mV. Thus, consistent with native T-type calcium channels, both of the α_{1G} and α_{1I} calcium channels exhibit pronounced steady-state inactivation at negative potentials.

Figs. 4A-C show a comparison of the voltage-dependent deactivation profiles of the α_{1G} and α_{1I} calcium channels. KEK 293 cells were transiently transfected with either an α_{1G} or α_{1I} subunit cDNA (Seq. ID No. 23 or 27). The deactivation properties of α_{1G} were determined by stepping from a holding potential of -100 mV to -40mV for 9 msec, and then to potentials between -120 mV and -45 mV. The deactivation properties of α_{1I} were determined by stepping from a holding potential of -100 mV to -40 mV for 20 msec, and then to potentials between -120 mV and -45 mV. Both channels exhibit slow deactivation kinetics compared to typical high-threshold channels, and is consistent with the α_{1G} and α_{1I} subunits being subunits for T-type calcium channels

What is claimed is:

1. An at least partially purified DNA molecule comprising a sequence of nucleotides that encodes an α_1 subunit of a mammalian T-type calcium channel.

2. The DNA molecule of claim 1, wherein the sequence of nucleotides is selected from sequences of nucleotides encoding a protein including the sequence of amino acids set forth in SEQ ID. No. 18, 20, 24, 26, 28, 31, 33, or 35 and sequences of nucleotides that hybridize under conditions of medium hybridization stringency to DNA encoding a protein including the sequence set forth in SEQ ID No. 18, 20, 24, 26, 28, 31, 33, 35.

3. The DNA molecule of Claim 1, wherein the calcium channel is a human calcium channel.

4. The DNA molecule of claim 1, further comprising a promoter region effective to promote expression of the α_1 subunit of a mammalian T-type calcium channel when the DNA molecule is transfected into a vertebrate cell.

5. The DNA molecule of claim 1, having the sequence as set forth in Seq. ID. No. 23, 25 or 27.

6. The DNA molecule of claim 1, wherein the molecule comprises a region consisting of the sequence as set forth in Seq. ID. No. 30, 32 or 34.

7. An at least partially purified α_1 subunit of a mammalian T-type calcium channel.

8. The α_1 subunit of claim 7 , wherein the subunit has the sequence as set forth in Seq. ID No. 24, 26 or 28 .

9. The α_1 subunit of claim 7 , wherein the subunit comprises a region consisting of the sequence as set forth in Seq. ID. No. 31, 33 or 35.

10. A eukaryotic cell transiently or stably transformed with the vertebrate expression vector comprising a sequence of nucleotides that encodes an α_1 subunit of a mammalian T-type calcium channel, wherein the cell expresses the α_1 subunit of a mammalian T-type calcium channel.

11. The cell of claim 10 , wherein the sequence of nucleotides is selected from sequences of nucleotides encoding a protein including the sequence of amino acids set forth in SEQ ID. No. 18, 20, 24, 26, 28, 31, 33, or 35, and sequences of nucleotides that hybridize under conditions of medium hybridization stringency to DNA encoding a protein including the sequence set forth in SEQ ID No. 18, 20, 24, 26, 28, 31, 33, or 35.

12. The cell of claim 10 , wherein the calcium channel is a human calcium channel.

13. The cell of claim 10 , wherein the sequence of nucleotides has the sequence as set forth in Seq. ID. No. 23, 25 or 27 .

14. The cell of claim 10 , wherein the sequence of nucleotides comprises a region consisting of the sequence as set forth in Seq. ID. No. 30, 32 or 34.

15. The cell of claim 10 , wherein the sequence of nucleotides has the sequence as set forth in Seq. ID. No. 27.

16. The cell of claim 10 , wherein the cell is further transformed with and expresses an $\alpha 2\delta$ or a β calcium channel subunit, or both.

17. A eukaryotic cell transiently or stably transformed with a heterologous DNA fragment comprising a sequence of nucleotides that encodes an α_1 subunit of a mammalian T-type calcium channel, wherein the cell expresses the α_1 subunit of a mammalian T-type calcium channel.

18. The cell of claim 17 , wherein the cell is further transformed with and expresses an $\alpha 2\delta$ or a β calcium channel subunit, or both.

19. A method for the production of an α-$_1$ subunit of a mammalian T-type calcium channel comprising, culturing a cell transiently or stably transformed or transfected with DNA encoding the calcium channel subunit under conditions such that the DNA is expressed and the α-$_1$ subunit is produced.

20. A process for producing a eukaryotic cell that is transiently or stably transformed and expresses a mammalian T-type calcium channel, comprising the step of introducing RNA or DNA encoding an α_1 subunit of a mammalian T-type calcium channel.

21. A method of identifying compounds capable of acting as agonists or antagonists for T-type mammalian calcium channels, comprising contacting a recombinant cell expressing a heterologous α_1 subunit of a mammalian T-type calcium channel, with an agent to be tested, and evaluating the interaction, if any, between the agent to be tested and the calcium channel.

22. An isolated DNA fragment having the sequence given by SEQ ID No. 19, 27 or 29.

23. A method for mapping the distribution of T-type calcium channels within a tissue sample comprising the steps of exposing the tissue to a reagent comprising a directly- or indirectly-detectable label coupled to a DNA fragment comprising a sequence selected from among those sequences given by SEQ ID Nos. 13-17, 19, 23, 25, 27, 29, 30, 32 and 34, and detecting reagent that has bound to the tissue.

24. A DNA fragment comprising a sequence of oligonucleotide that encodes a calcium channel, wherein the sequence of nucleotides is selected from sequences of nucleotides encoding a protein including the sequence of amino acids set forth in SEQ ID. No. 18, 20, 24, 26, 28, 31, 33, or 35, or a nucleotide sequence obtainable by subcloning a PCR product of SEQ ID Nos: 13, 14, 15, or 16, labeling it by random hexamer priming, using the primer to screen a commercial human brain cDNA library to produce partial sequence clones containing overlapping cDNAs and ligating cDNAs obtained to produce full length cDNA encoding a calcium channel protein.

ABSTRACT OF THE DISCLOSURE

Sequences and partial sequences for three types of mammalian (human and rat sequences identified) T-type calcium channel subunits which we have labeled as the α_{1G}, α_{1H} and α_{1I} subunits are provided. Knowledge of the sequence of these calcium channel permits the localization and recovery of the complete sequence from human cells, and the development of cell lines which express the novel calcium channels of the invention. These cells may be used for identifying compounds capable of acting as agonists or antagonists to the calcium channels.

NMED.P-001-2
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Snutch et al.

Serial No.: to be assigned

Filed: herewith

For: NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

Statement Regarding Sequence Listing

Asst. Commissioner for Patents

Washington, D.C. 20231

Sir:

The undersigned hereby certifies that the paper copy of the sequence listing and the machine readable diskette filed herewith contain the same information.

Respectfully submitted,

Marina T. Larson
PTO Reg. No. 32,038
Attorney for Applicant
(970) 668-2050

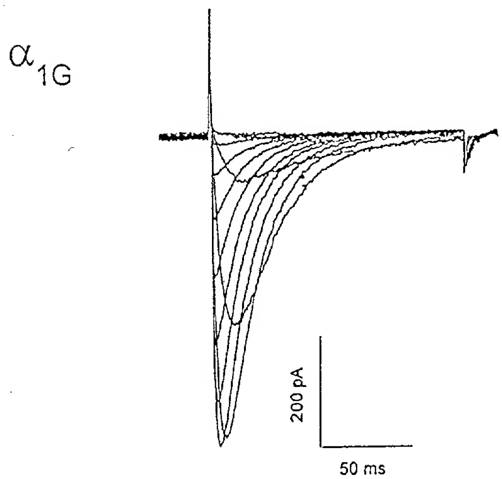
α1G
200 pA
50 ms

Fig. 1A

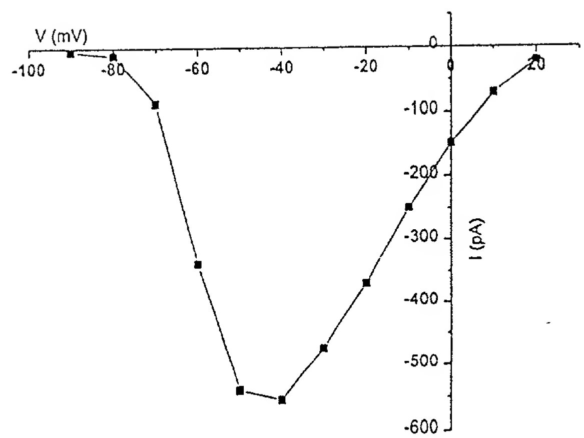
V (mV)
-100
-80
-60
-40
-20
0
20
0
-100
-200
-300
-400
-500
-600
I (pA)

Fig. 1B

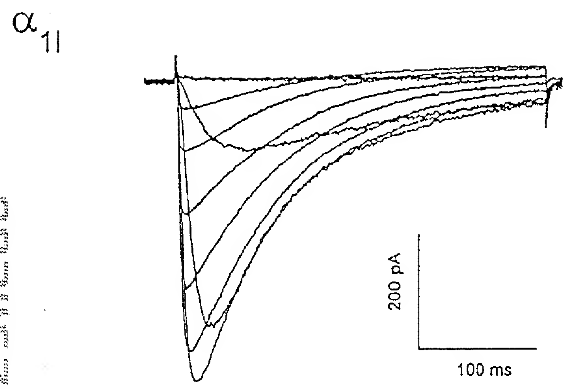
α1I
200 pA
100 ms

Fig. 2A

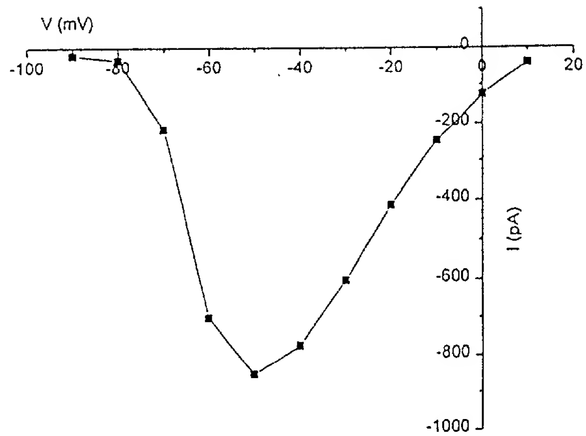
V (mV)
-100
-80
-60
-40
-20
0
20
0
-200
-400
-600
-800
-1000
I (pA)

Fig. 2 B

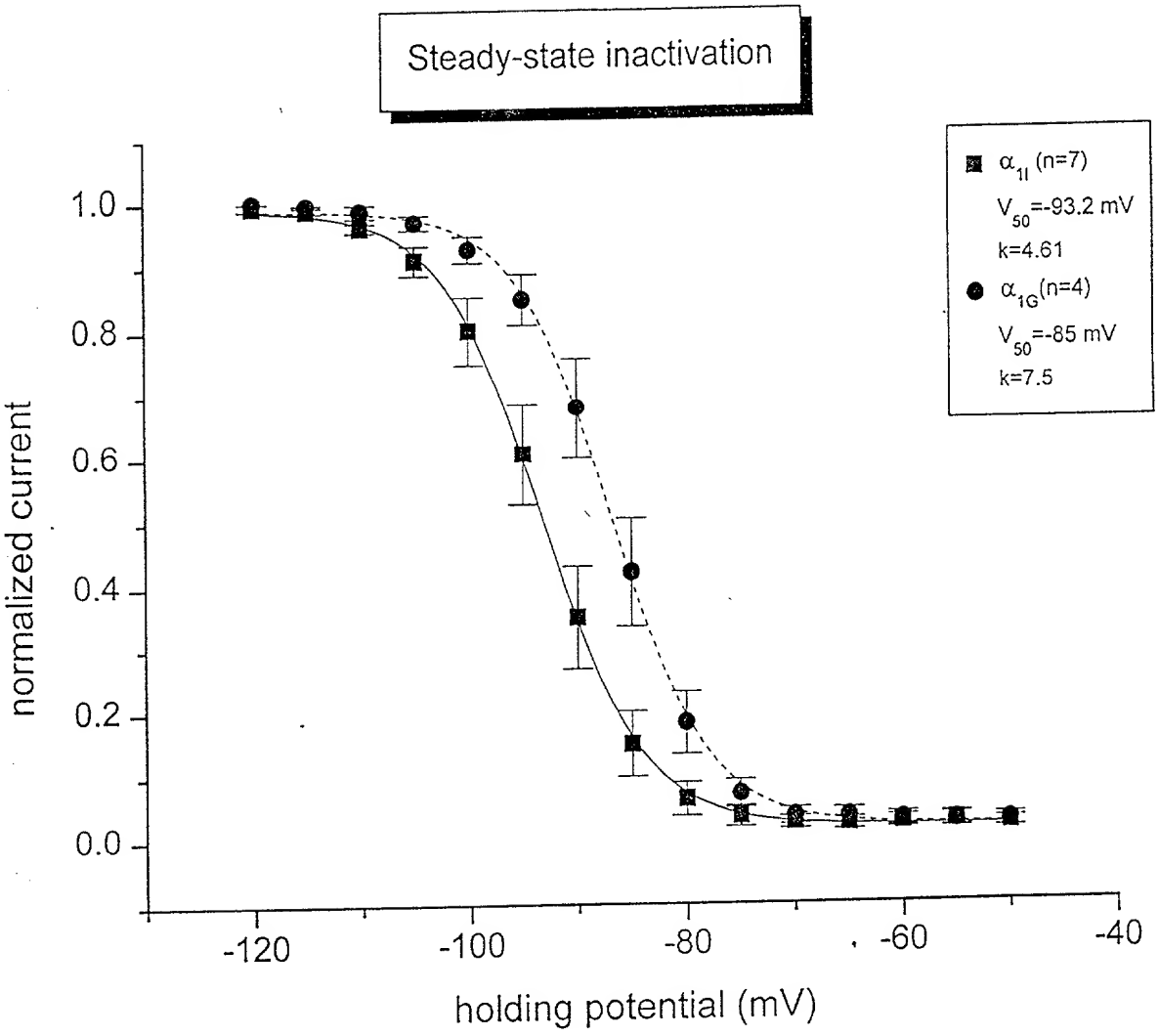
Steady-state inactivation
α_{1I} (n=7)
V_{50}=-93.2 mV
k=4.61
α_{1G}(n=4)
V_{50}=-85 mV
k=7.5
normalized current
1.0
0.8
0.6
0.4
0.2
0.0
-120
-100
-80
-60
-40
holding potential (mV)

Fig. 3

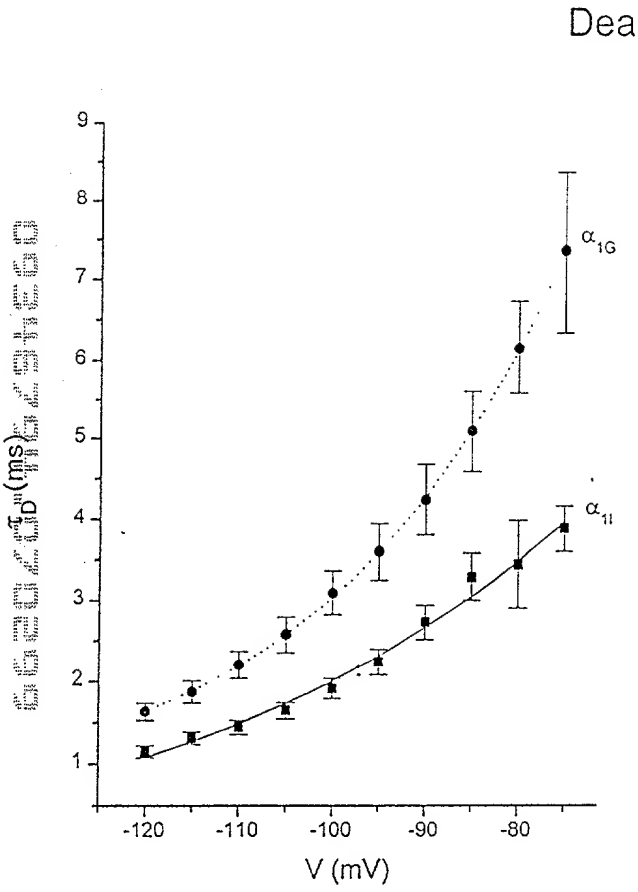

Fig. 4A

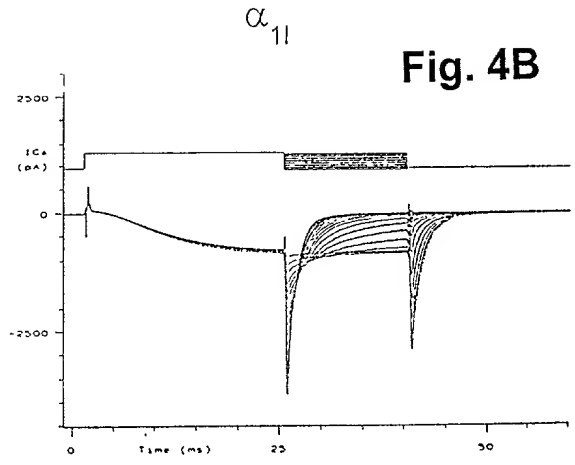

Fig. 4B

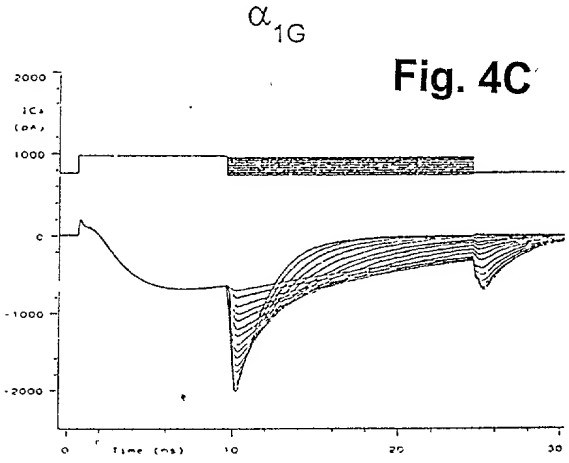

Fig. 4C

SEQUENCE LISTING

<110> Snutch, Terry P.
Baillie, David L.

<120> NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

<130> NMED.P-001-2(CIP)

<140>
<141>

<150> 09/030,482
<151> 1998-02-25

<150> 60/039,204
<151> 1997-02-28

<160> 35

<170> PatentIn Ver. 2.0

<210> 1
<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 1
gtcaaaactc aggccttcta ctgg 24

<210> 2
<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 2
aacgtgttct tggctatcgc ggtg 24

<210> 3

<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 3
gtgaaagcac agagcttcta ctgg 24

<210> 4
<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 4
aacgttttct tggccattgc tgtg 24

<210> 5
<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 5
gttaaatcca acgtcttcta ctgg 24

<210> 6
<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 6
aatgtgttct tggccattgc ggtg 24

<210> 7

<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 7
gtgaagtctg tcacgtttta ctgg 24

<210> 8
<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 8
aagctcttct tggccattgc tgta 24

<210> 9
<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 9
gtcaagtcgc aagtgttcta ctgg 24

<210> 10
<211> 24
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 10
aatgtattct tggctatcgc tgtg 24

<210> 11

<211> 21
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 11
atctaygcyr tsatyggsat g 21

<210> 12
<211> 20
<212> DNA
<213> rat

<220>
<223> oligonucleotide probe for locating calcium channel genes

<400> 12
atggacaayt tygastaytc 20

<210> 13
<211> 168
<212> DNA
<213> HUMAN

<220>
<223> expressed sequence tag H55225

<400> 13
gtgatcactc tggaaggctg ggtggagatc atgtactacg tgatggatgc tcactccttc 60
tacaacttca tctacttcat cctgcttatc ataccctct tgccttgcac cccatatggt 120
cttcccagag tgagctcatc cacctcgtca tgcctgactc gacgttca 168

<210> 14
<211> 98
<212> DNA
<213> HUMAN

<220>
<223> expressed sequence tag H55617

<400> 14
gatggtcgag tactccctgg accttcagaa catcaacctg tcagccatcc gcaccgtgcg 60
cgtcctgagg cccctcaaag ccatcaaccg cgtgccca 98

<210> 15
<211> 94
<212> DNA
<213> HUMAN

<220>
<223> expressed sequence tag H55223

<400> 15
catgctggtg atcctgctga actgcgtgac acttggcatg taccagccgt gcgacgacat 60
ggactgcctg tccgaccgct gcaagatcct gcag 94

<210> 16
<211> 123
<212> DNA
<213> HUMAN

<220>
<223> expressed sequence tag H55544

<400> 16
gtatctctgg ttactttagt agccaacact cttggctact cagaccttgg tcccattaaa 60
tccctgcgaa ccttgagagc actaagacct ctaagagctt tgtctagatt tgaaggaatg 120
agg 123

<210> 17
<211> 5562
<212> DNA
<213> HUMAN

<220>
<223> human alpha-I partial sequence from BAC bK206c7

<400> 17
atgtttttcg tctcagccaa tccctgggtg agtttcacca gttttgattt aaacgtggcc 60
aatatggaca acttcttcgc ccccgttttc accatgggca aatattatac gcaaggcgac 120
aaggtgctga tgccgctggc gattcaggct ctgaaacagc tgatgttcaa attggtggcc 180
actgttgctc gaacacatgc tacaccgtca cacatcacgg gtggtcctgg aacagggatg 240
cacacgggca ccttccagga aggagctgag cctggttcat ctcagcaccc tgaggcacag 300
gccacgtata cagcagggtg caccccagcc cccacgggcg atcccacctg ctgctttgtc 360
cttgacttgg tgtgcacgtg gtttgaatgt gtcagcatgc tggtgatcct gctgaactgc 420
gtgacacttg gcatgtacca gccgtgcgac gacatggact gcctgtccga ccgctgcaag 480
atcctgcagg tctttgatga cttcatcttt atcttctttg ccatggagat ggtgctcaag 540
atggtggccc tggggatttt tggcaagaag tgctacctcg gggacacatg gaaccgcctg 600
gatttcttca tcgtcatggc aggcaacatc aacctgtcag ccatccgcac cgtgcgcgtc 660
ctgaggcccc tcaaagccat caaccgcgtg cccagtatgc ggatcctggt gaacctgctc 720
ctggacacac tgcccatgct ggggaatgtc ctgctgctct gcttctttgt cttcttcatc 780
tttggcatca taggtgtgca gctctgggcg ggcctgctgc gtaaccgctg cttcctggag 840

gagaacttca ccatacaagg ggatgtggcc ttgccccat actaccagcc ggaggaggat 900
gatgagatgc ccttcatctg ctccctgtcg ggcgacaatg ggataatggg ctgccatgag 960
atccccccgc tcaaggagca gggccgtgag tgctgcctgt ccaaggacga cgtctacgac 1020
tttggggcgg ggcgccagga cctcaatgcc agcggcctct gtgtcaactg gaaccgttac 1080
tacaatgtgt gccgcacggg cagcgccaac ccccacaagg gtgccatcaa ctttgacaac 1140
atcggttatg cttggattgt catcttccag gtgatcactc tggaaggctg ggtggagatc 1200
atgtactacg tgatggatgc tcactccttc tacaacttca tctacttcat cctgcttatc 1260
ataagtgagc tcatccacct cgtcatgcct gactgcagct tcagcacagc acagtcccca 1320
aaatgtcaag gtgattcact cccaggagtc gctgctgaat ccctgctgct gcgagactct 1380
agctcctcag tcatcactga tgaggctgca gccatggaga acctcctggc gggcacctcc 1440
aaggggggatg aaagctatct gctcaggctg gccggcagcc aagttcactc ccaggctcag 1500
caaatgctgg ggaggggggct gggccctgaa agcctggaaa ctggagagga gccccactcg 1560
tggagccctc gggccacaag gagatgggat ccccaatgcc aaccagggca gcctctcccc 1620
cttcatttca tgcaagcaca ggtgggctcc ttcttcatga tcaacctgtg cctcgttgtc 1680
atagcgaccc agttctcgga gaccaagcaa cgggagcacc ggctgatgct ggagcagcgg 1740
cagcgctacc tgtcctccag cacggtggcc agctacgccg agcctggcga ctgctacgag 1800
gagatcttcc agtatgtctg ccacatcctg cgcaaggcca agcgccgcgc cctgggcctc 1860
taccaggccc tgcagagccg gcgccaggcc ctgggcccgg aggccccggc ccccgccaaa 1920
cctgggcccc acgccaagga gccccggcac taccctctca cagtctggga atcgattctt 1980
gggaggcaag cagaagaatg cacgctcaga gctgccgccc acccgtcctc gggtgccagc 2040
catccaggcg tgggctcgga ggaggcccca gagctgtgcc cgcaacatag ccccctggat 2100
gcgacgcccc acaccctggt gcagcccatc cccgccacgc tggcttccga tcccgccagc 2160
tgcccttgct gccagcatga ggacggccgg cggccctcgg gcctgggcag caccgactcg 2220
ggccaggagg gctcgggctc cgggagctcc gctggtggcg aggacgaggc ggatggggac 2280
ggggcccgga gcagcgagga cggagcctcc tcagaactgg ggaaggagga ggaggaggag 2340
gagcaggcgg atggggcggt ctggctgtgc ggggatgtgt ggcgggagac gcgagccaag 2400
ctgcgcggca tcgtggacag caagtacttc aaccggggca tcatgatggc catcctggtc 2460
aacaccgtca gcatgggcat cgagcaccac gagcaggcca gtgcagcgca gccgggccgg 2520
gcctgcggga gaggacaaaa tccagacctt tgcatgaccc tcaaggcccc ttgtctctgt 2580
cacaacgtcc cttcaccagg ccagggtgtc ctgtcccatc cagtgactcc accccataca 2640
gccccatggc gcatggagac aggaaagcag ggacacggat gtgaagaagg accaggacaa 2700
cgaagcagtg acatgtttgc cctggagatg atcctgaagc tggctgcatt tgggctcttc 2760
gactacctgc gtaaccccta caacatcttc gacagcatca ttgtcatcat cagcatctgg 2820
gagatcgtgg ggcaggcgga cggtgggctg tcggtgctgc ggaccttccg gctgctgcgc 2880
gtgctgaaac tggtgcgctt catgcctgcc ctgcggcgcc agctcgtggt gctcatgaag 2940
accatggaca acgtggccac cttctgcatg ctgctcatgc tcttcatctt catcttcagc 3000
atccttggga tgcatatttt tggctgcaag ttcagcctcc gcacggacac tggagacacg 3060
gtgcccgaca ggaagaactt cgactccctg ctgtgggcca tcgtcactgt gttccagatc 3120
ctcacccagg aggactggaa cgtcgttctc tacaatggca tggcctccac ttctccctgg 3180
gcctccctct actttgtcgc cctcatgacc ttcggcaact atgtgctctt caacctgctg 3240
gtggccatcc tggtggaggg cttccaggcg gaggtgactg tggtcttggc agaggaagca 3300
cccccacagg gcctgcgaaa gactgggcga gggagaggtg gcctggatgg gggagggctg 3360
caattcaaac ttctagcagg caacctatcc ctaaaggagg gggttgctga tgaggtgggt 3420
gacgccaatc gctcctactc ggacgaggac cagagctcat ccaacataga agagtttgat 3480
aagctccagg aaggcctgga cagcagcgga gatcccaagc tctgcccaat ccccatgacc 3540
cccaatgggc acctggaccc cagtctccca ctgggtgggc acctaggtcc tgctggggct 3600
gcgggacctg ccccccgact ctcactgcag ccggacccca tgctggtggc cctgggctcc 3660
cgaaagagca gcgtcatgtc tctagggagg atgagctatg accagcgctc cctggtgggt 3720

ggtcttagag ccacagcggg ggtgcaggct gcctttgggc acctggtgcc ccagccgtgg 3780
gtgtgcctgt ggggcgctga cccgaacggg aactccttcc agtccagctc ccggagctcc 3840
tactacgggc catggggccg cagcgcggcc tgggccagcc gtcgctccag ctggaacagc 3900
ctcaagcaca agccgccgtc ggcggagcat gagtccctgc tctctgcgga gcgcggcggc 3960
ggcgcccggg tctgcgaggt tgccgcggac gaggggccgc cgcgggccgc acccctgcac 4020
accccacacg cccaccacgt tcatcacggg ccccatctgg cgcaccgcca ccgccaccac 4080
cgccggacgc tgtccctcga caacagggac tcggtggacc tggccgagct ggtgcccgcg 4140
gtgggcgccc acccccgggc cgcctggagg gcggcaggcc cggcccccgg gcatgaggac 4200
tgcaatggca ggatgcccag catcgccaaa gacgtcttca ccaagatggg cgaccgcggg 4260
gatcgcgggg aggatgagga ggaaatcgac tacgtgagtg ggggcggggc cgaaggggac 4320
ctgaccctgt gcttccgcgt ccgcaagatg atcgacgtct ataagcccga ctggtgcgag 4380
gtccgcgaag actggtctgt ctacctcttc tctcccgaga acaggctcag ggatctgggc 4440
tgggtaagcc tcgagtgcca gggaaaggtg ggtgacctcg tggtgtgggt gtatggtcag 4500
aggaggcagc gccagaccat tattgcccac aaactcttcg actacgtcgt cctggccttc 4560
atctttctca actgcatcac catcgccctg gagcggcctc agatcgaggc cggcagcacc 4620
gaacgcatct ttctcaccgt gtccaactac atcttcacgg ccatcttcgt gggcgagatg 4680
acattgaagg tagtctcgct gggcctgtac ttcggcgagc aggcgtacct acgcagcagc 4740
tggaacgtgc tggatggctt tcttgtcttc gtgtccatca tcgacatcgt ggtgtccctg 4800
gcctcagccg ggggagccaa gatcttgggg gtcctccgag tcttgcggct cctgcgcacc 4860
ctacgccccc tgcgtgtcat cagccgggcg ccgggcctga agctggtggt ggagacactc 4920
atctcctccc tcaagcccat cggcaacatc gtgctcatct gctgtgcctt cttcatcatc 4980
tttggcatcc tgggagtgca gctcttcaag ggcaagttct accactgtct gggcgtggac 5040
acccgcaaca tcaccaaccg ctcggactgc atggccgcca actaccgctg ggtccatcac 5100
aaatacaact tcgacaacct gggccaggct ctgatgtccc tctttgtcct ggcatccaag 5160
gatggttggg tgaacatcat gtacaatgga ctggatgctg ttgctgtgga ccagcagcct 5220
gtgaccaacc acaacccctg gatgctgctg tacttcatct ccttcctgct catcgtcagc 5280
ttctttgtgc tcaacatgtt tgtgggtgtc gtggtggaga acttccacaa gtgccggcag 5340
caccaggagg ctgaagaggc acggcggcgt gaggagaagc ggctgcggcg cctggagaag 5400
aagcgccgga aggcccagcg gctgccctac tatgccacct attgtcacac ccggctgctc 5460
atccactcca tgtgcaccag ccactacctg gacatcttca tcaccttcat catctgcctc 5520
aacgtggtca ccatgtccct ggagcactac aatcagccca cg 5562

<210> 18
<211> 1854
<212> PRT
<213> HUMAN

<220>
<223> human alpha-I partial sequence from BAC bK206c7

<400> 18
Met Phe Phe Val Ser Ala Asn Pro Trp Val Ser Phe Thr Ser Phe Asp
1 5 10 15

Leu Asn Val Ala Asn Met Asp Asn Phe Phe Ala Pro Val Phe Thr Met
20 25 30

Gly Lys Tyr Tyr Thr Gln Gly Asp Lys Val Leu Met Pro Leu Ala Ile

35 40 45

Gln Ala Leu Lys Gln Leu Met Phe Lys Leu Val Ala Thr Val Ala Arg
50 55 60

Thr His Ala Thr Pro Ser His Ile Thr Gly Gly Pro Gly Thr Gly Met
65 70 75 80

His Thr Gly Thr Phe Gln Glu Gly Ala Glu Pro Gly Ser Ser Gln His
85 90 95

Pro Glu Ala Gln Ala Thr Tyr Thr Ala Gly Cys Thr Pro Ala Pro Thr
100 105 110

Gly Asp Pro Thr Cys Cys Phe Val Leu Asp Leu Val Cys Thr Trp Phe
115 120 125

Glu Cys Val Ser Met Leu Val Ile Leu Leu Asn Cys Val Thr Leu Gly
130 135 140

Met Tyr Gln Pro Cys Asp Asp Met Asp Cys Leu Ser Asp Arg Cys Lys
145 150 155 160

Ile Leu Gln Val Phe Asp Asp Phe Ile Phe Ile Phe Phe Ala Met Glu
165 170 175

Met Val Leu Lys Met Val Ala Leu Gly Ile Phe Gly Lys Lys Cys Tyr
180 185 190

Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val Met Ala Gly
195 200 205

Asn Ile Asn Leu Ser Ala Ile Arg Thr Val Arg Val Leu Arg Pro Leu
210 215 220

Lys Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Asn Leu Leu
225 230 235 240

Leu Asp Thr Leu Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe
245 250 255

Val Phe Phe Ile Phe Gly Ile Ile Gly Val Gln Leu Trp Ala Gly Leu
260 265 270

Leu Arg Asn Arg Cys Phe Leu Glu Glu Asn Phe Thr Ile Gln Gly Asp
275 280 285

Val Ala Leu Pro Pro Tyr Tyr Gln Pro Glu Glu Asp Asp Glu Met Pro

290 295 300

Phe Ile Cys Ser Leu Ser Gly Asp Asn Gly Ile Met Gly Cys His Glu
305 310 315 320

Ile Pro Pro Leu Lys Glu Gln Gly Arg Glu Cys Cys Leu Ser Lys Asp
325 330 335

Asp Val Tyr Asp Phe Gly Ala Gly Arg Gln Asp Leu Asn Ala Ser Gly
340 345 350

Leu Cys Val Asn Trp Asn Arg Tyr Tyr Asn Val Cys Arg Thr Gly Ser
355 360 365

Ala Asn Pro His Lys Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala
370 375 380

Trp Ile Val Ile Phe Gln Val Ile Thr Leu Glu Gly Trp Val Glu Ile
385 390 395 400

Met Tyr Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe
405 410 415

Ile Leu Leu Ile Ile Ser Glu Leu Ile His Leu Val Met Pro Asp Cys
420 425 430

Ser Phe Ser Thr Ala Gln Ser Pro Lys Cys Gln Gly Asp Ser Leu Pro
435 440 445

Gly Val Ala Ala Glu Ser Leu Leu Leu Arg Asp Ser Ser Ser Ser Val
450 455 460

Ile Thr Asp Glu Ala Ala Ala Met Glu Asn Leu Leu Ala Gly Thr Ser
465 470 475 480

Lys Gly Asp Glu Ser Tyr Leu Leu Arg Leu Ala Gly Ser Gln Val His
485 490 495

Ser Gln Ala Gln Gln Met Leu Gly Arg Gly Leu Gly Pro Glu Ser Leu
500 505 510

Glu Thr Gly Glu Glu Pro His Ser Trp Ser Pro Arg Ala Thr Arg Arg
515 520 525

Trp Asp Pro Gln Cys Gln Pro Gly Gln Pro Leu Pro Leu His Phe Met
530 535 540

Gln Ala Gln Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val Val

545 550 555 560

Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu His Arg Leu Met
565 570 575

Leu Glu Gln Arg Gln Arg Tyr Leu Ser Ser Ser Thr Val Ala Ser Tyr
580 585 590

Ala Glu Pro Gly Asp Cys Tyr Glu Glu Ile Phe Gln Tyr Val Cys His
595 600 605

Ile Leu Arg Lys Ala Lys Arg Arg Ala Leu Gly Leu Tyr Gln Ala Leu
610 615 620

Gln Ser Arg Arg Gln Ala Leu Gly Pro Glu Ala Pro Ala Pro Ala Lys
625 630 635 640

Pro Gly Pro His Ala Lys Glu Pro Arg His Tyr Pro Leu Thr Val Trp
645 650 655

Glu Ser Ile Leu Gly Arg Gln Ala Glu Glu Cys Thr Leu Arg Ala Ala
660 665 670

Ala His Pro Ser Ser Gly Ala Ser His Pro Gly Val Gly Ser Glu Glu
675 680 685

Ala Pro Glu Leu Cys Pro Gln His Ser Pro Leu Asp Ala Thr Pro His
690 695 700

Thr Leu Val Gln Pro Ile Pro Ala Thr Leu Ala Ser Asp Pro Ala Ser
705 710 715 720

Cys Pro Cys Cys Gln His Glu Asp Gly Arg Arg Pro Ser Gly Leu Gly
725 730 735

Ser Thr Asp Ser Gly Gln Glu Gly Ser Gly Ser Gly Ser Ser Ala Gly
740 745 750

Gly Glu Asp Glu Ala Asp Gly Asp Gly Ala Arg Ser Ser Glu Asp Gly
755 760 765

Ala Ser Ser Glu Leu Gly Lys Glu Glu Glu Glu Glu Glu Gln Ala Asp
770 775 780

Gly Ala Val Trp Leu Cys Gly Asp Val Trp Arg Glu Thr Arg Ala Lys
785 790 795 800

Leu Arg Gly Ile Val Asp Ser Lys Tyr Phe Asn Arg Gly Ile Met Met

805 810 815

Ala Ile Leu Val Asn Thr Val Ser Met Gly Ile Glu His His Glu Gln
820 825 830

Ala Ser Ala Ala Gln Pro Gly Arg Ala Cys Gly Arg Gly Gln Asn Pro
835 840 845

Asp Leu Cys Met Thr Leu Lys Ala Pro Cys Leu Cys His Asn Val Pro
850 855 860

Ser Pro Gly Gln Gly Val Leu Ser His Pro Val Thr Pro Pro His Thr
865 870 875 880

Ala Pro Trp Arg Met Glu Thr Gly Lys Gln Gly His Gly Cys Glu Glu
885 890 895

Gly Pro Gly Gln Arg Ser Ser Asp Met Phe Ala Leu Glu Met Ile Leu
900 905 910

Lys Leu Ala Ala Phe Gly Leu Phe Asp Tyr Leu Arg Asn Pro Tyr Asn
915 920 925

Ile Phe Asp Ser Ile Ile Val Ile Ile Ser Ile Trp Glu Ile Val Gly
930 935 940

Gln Ala Asp Gly Gly Leu Ser Val Leu Arg Thr Phe Arg Leu Leu Arg
945 950 955 960

Val Leu Lys Leu Val Arg Phe Met Pro Ala Leu Arg Arg Gln Leu Val
965 970 975

Val Leu Met Lys Thr Met Asp Asn Val Ala Thr Phe Cys Met Leu Leu
980 985 990

Met Leu Phe Ile Phe Ile Phe Ser Ile Leu Gly Met His Ile Phe Gly
995 1000 1005

Cys Lys Phe Ser Leu Arg Thr Asp Thr Gly Asp Thr Val Pro Asp Arg
1010 1015 1020

Lys Asn Phe Asp Ser Leu Leu Trp Ala Ile Val Thr Val Phe Gln Ile
1025 1030 1035 1040

Leu Thr Gln Glu Asp Trp Asn Val Val Leu Tyr Asn Gly Met Ala Ser
1045 1050 1055

Thr Ser Pro Trp Ala Ser Leu Tyr Phe Val Ala Leu Met Thr Phe Gly

1060 1065 1070

Asn Tyr Val Leu Phe Asn Leu Leu Val Ala Ile Leu Val Glu Gly Phe
1075 1080 1085

Gln Ala Glu Val Thr Val Val Leu Ala Glu Glu Ala Pro Pro Gln Gly
1090 1095 1100

Leu Arg Lys Thr Gly Arg Gly Arg Gly Gly Leu Asp Gly Gly Gly Leu
1105 1110 1115 1120

Gln Phe Lys Leu Leu Ala Gly Asn Leu Ser Leu Lys Glu Gly Val Ala
1125 1130 1135

Asp Glu Val Gly Asp Ala Asn Arg Ser Tyr Ser Asp Glu Asp Gln Ser
1140 1145 1150

Ser Ser Asn Ile Glu Glu Phe Asp Lys Leu Gln Glu Gly Leu Asp Ser
1155 1160 1165

Ser Gly Asp Pro Lys Leu Cys Pro Ile Pro Met Thr Pro Asn Gly His
1170 1175 1180

Leu Asp Pro Ser Leu Pro Leu Gly Gly His Leu Gly Pro Ala Gly Ala
1185 1190 1195 1200

Ala Gly Pro Ala Pro Arg Leu Ser Leu Gln Pro Asp Pro Met Leu Val
1205 1210 1215

Ala Leu Gly Ser Arg Lys Ser Ser Val Met Ser Leu Gly Arg Met Ser
1220 1225 1230

Tyr Asp Gln Arg Ser Leu Val Gly Gly Leu Arg Ala Thr Ala Gly Val
1235 1240 1245

Gln Ala Ala Phe Gly His Leu Val Pro Gln Pro Trp Val Cys Leu Trp
1250 1255 1260

Gly Ala Asp Pro Asn Gly Asn Ser Phe Gln Ser Ser Ser Arg Ser Ser
1265 1270 1275 1280

Tyr Tyr Gly Pro Trp Gly Arg Ser Ala Ala Trp Ala Ser Arg Arg Ser
1285 1290 1295

Ser Trp Asn Ser Leu Lys His Lys Pro Pro Ser Ala Glu His Glu Ser
1300 1305 1310

Leu Leu Ser Ala Glu Arg Gly Gly Gly Ala Arg Val Cys Glu Val Ala

1315 1320 1325

Ala Asp Glu Gly Pro Pro Arg Ala Ala Pro Leu His Thr Pro His Ala
1330 1335 1340

His His Val His His Gly Pro His Leu Ala His Arg His Arg His His
1345 1350 1355 1360

Arg Arg Thr Leu Ser Leu Asp Asn Arg Asp Ser Val Asp Leu Ala Glu
1365 1370 1375

Leu Val Pro Ala Val Gly Ala His Pro Arg Ala Ala Trp Arg Ala Ala
1380 1385 1390

Gly Pro Ala Pro Gly His Glu Asp Cys Asn Gly Arg Met Pro Ser Ile
1395 1400 1405

Ala Lys Asp Val Phe Thr Lys Met Gly Asp Arg Gly Asp Arg Gly Glu
1410 1415 1420

Asp Glu Glu Glu Ile Asp Tyr Val Ser Gly Gly Gly Ala Glu Gly Asp
1425 1430 1435 1440

Leu Thr Leu Cys Phe Arg Val Arg Lys Met Ile Asp Val Tyr Lys Pro
1445 1450 1455

Asp Trp Cys Glu Val Arg Glu Asp Trp Ser Val Tyr Leu Phe Ser Pro
1460 1465 1470

Glu Asn Arg Leu Arg Asp Leu Gly Trp Val Ser Leu Glu Cys Gln Gly
1475 1480 1485

Lys Val Gly Asp Leu Val Val Trp Val Tyr Gly Gln Arg Arg Gln Arg
1490 1495 1500

Gln Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val Leu Ala Phe
1505 1510 1515 1520

Ile Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro Gln Ile Glu
1525 1530 1535

Ala Gly Ser Thr Glu Arg Ile Phe Leu Thr Val Ser Asn Tyr Ile Phe
1540 1545 1550

Thr Ala Ile Phe Val Gly Glu Met Thr Leu Lys Val Val Ser Leu Gly
1555 1560 1565

Leu Tyr Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu

1570 1575 1580

Asp Gly Phe Leu Val Phe Val Ser Ile Ile Asp Ile Val Val Ser Leu
1585 1590 1595 1600

Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg Val Leu Arg
1605 1610 1615

Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Pro Gly
1620 1625 1630

Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Lys Pro Ile Gly
1635 1640 1645

Asn Ile Val Leu Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu
1650 1655 1660

Gly Val Gln Leu Phe Lys Gly Lys Phe Tyr His Cys Leu Gly Val Asp
1665 1670 1675 1680

Thr Arg Asn Ile Thr Asn Arg Ser Asp Cys Met Ala Ala Asn Tyr Arg
1685 1690 1695

Trp Val His His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met
1700 1705 1710

Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asn Ile Met Tyr
1715 1720 1725

Asn Gly Leu Asp Ala Val Ala Val Asp Gln Gln Pro Val Thr Asn His
1730 1735 1740

Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ser
1745 1750 1755 1760

Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His
1765 1770 1775

Lys Cys Arg Gln His Gln Glu Ala Glu Glu Ala Arg Arg Arg Glu Glu
1780 1785 1790

Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Lys Ala Gln Arg Leu
1795 1800 1805

Pro Tyr Tyr Ala Thr Tyr Cys His Thr Arg Leu Leu Ile His Ser Met
1810 1815 1820

Cys Thr Ser His Tyr Leu Asp Ile Phe Ile Thr Phe Ile Ile Cys Leu

1825 1830 1835 1840

Asn Val Val Thr Met Ser Leu Glu His Tyr Asn Gln Pro Thr
1845 1850

<210> 19
<211> 567
<212> DNA
<213> HUMAN

<220>
<223> human alpha-I partial sequence

<400> 19
atgcggatcc tggtgaacct gctcctggac acactgccca tgctggggaa tgtcctgctg 60
ctctgcttct ttgtcttctt cacctttggc atcataggtg tgcagctctg ggcgggcctg 120
ctgcgtaacc gctgcttcct ggaggagaac ttcaccatac aaggggatgt ggccttgccc 180
ccatactacc agccggagga ggatgatgag atgcccttca tctgctccct gtcgggcgac 240
aatgggataa tgggctgcca tgagatcccc ccgctcaagg agcagggccg tgagtgctgc 300
ctgtccaagg acgacgtcta cgactttggg gcggggcgcc aggacctcaa tgccagcggc 360
ctctgtgtca actggaaccg ttactacaat gtgtgccgca cgggcagcgc caacccccac 420
aagggtgcca tcagctttga caacatcggt tatgcttgga ttgtcatctt ccaggtgatc 480
actctggaag gctgggtggc gatcatgtac tacgtgatgg atgctctctc cttctacaac 540
ttcgtctact tcatcctgct tatcata 567

<210> 20
<211> 189
<212> PRT
<213> HUMAN

<220>
<223> human alpha-I partial sequence

<400> 20
Met Arg Ile Leu Val Asn Leu Leu Leu Asp Thr Leu Pro Met Leu Gly
1 5 10 15

Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Thr Phe Gly Ile Ile
20 25 30

Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu Glu
35 40 45

Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
50 55 60

Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Ser Gly Asp

65 70 75 80

Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
85 90 95

Arg Glu Cys Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
100 105 110

Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
115 120 125

Tyr Asn Val Cys Arg Thr Gly Ser Ala Asn Pro His Lys Gly Ala Ile
130 135 140

Ser Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln Val Ile
145 150 155 160

Thr Leu Glu Gly Trp Val Ala Ile Met Tyr Tyr Val Met Asp Ala Leu
165 170 175

Ser Phe Tyr Asn Phe Val Tyr Phe Ile Leu Leu Ile Ile
180 185

<210> 21
<211> 567
<212> DNA
<213> rat

<220>
<223> rat alpha-I partial sequence

<400> 21
atgcggatcc tggtgaacct gctgctcgac acgctgccca tgctggggaa cgtgctcctg 60
ctctgtttct tcgtcttctt catcttcggc atcattggcg tgcagctctg ggcaggcctg 120
ctacggaacc gctgcttcct ggaagaaaac ttcaccatac aaggggatgt ggccctgccc 180
ccttattacc aaccagagga ggatgacgag atgcccttta tctgctccct gactggggac 240
aatggcatca tgggctgcca cgagatcccc ccactgaagg agcagggccg ggaatgctgc 300
ctgtccaaag atgatgtgta tgacttcggg gcggggcgcc aggacctcaa cgccagcggt 360
ctgtgcgtca actggaaccg ctactacaac gtctgccgca cgggcaacgc caaccctcac 420
aagggcgcca tcaactttga caacattggc tatgcctgga ttgtgatttt ccaggtgatc 480
actctggaag gctgggtgga gatcatgtac tatgtgatgg acgcacattc tttctacaac 540
ttcatctact tcatcctgct tatcata 567

<210> 22
<211> 189
<212> PRT
<213> rat

<220>
<223> rat alpha-I partial sequence

<400> 22

```
Met Arg Ile Leu Val Asn Leu Leu Leu Asp Thr Leu Pro Met Leu Gly
 1               5                  10                  15

Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile Phe Gly Ile Ile
            20                  25                  30

Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu Glu
        35                  40                  45

Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
    50                  55                  60

Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Thr Gly Asp
65                  70                  75                  80

Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
                85                  90                  95

Arg Glu Cys Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
            100                 105                 110

Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
        115                 120                 125

Tyr Asn Val Cys Arg Thr Gly Asn Ala Asn Pro His Lys Gly Ala Ile
    130                 135                 140

Asn Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln Val Ile
145                 150                 155                 160

Thr Leu Glu Gly Trp Val Glu Ile Met Tyr Tyr Val Met Asp Ala His
                165                 170                 175

Ser Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile
            180                 185
```

<210> 23
<211> 7540
<212> DNA
<213> rat

<400> 23

ccgtctctgg cgcggagcgg gacgatgctg acccccttaga tcctgctcca gctgcgccga 60
gggaagaggg ggcgcccctc cccggacccc cgccctccat cgggtggccc ctttttttttc 120
tcttcctctc gggggctgct tcgccgaagg tagcgcctgt tacgggcaac cggagcctgg 180
gcgcgaacga agaagccgga acaaagtgag gggaagccgc ccggctagtc ggggagcccc 240
cgggaaccca ggggaagcgg gactctacgc caggcggggc ttccctgaga cccggcgccc 300
cgcgggcagc atgccctgag ggcaggggga gctgagctga actggccctc ctggggactc 360
agcaagctct ctagagcccc ccacatgctc ccccaccggg tcccccgttg cgtgaggaca 420
cctcctctga ggggctccgc tcgcccctct tcggacccca cggggccccg gctggccaga 480
ggatggacga ggaggaggat ggagcgggcg ccgaggagtc gggacagccc cgtagcttca 540
cgcagctcaa cgacctgtcc ggggccgggg gcggcagggg ccgggtcgac ggaaaaggac 600
ccgggcagcg cggactccga ggcggagggg ctgccgtacc cggcgctagc cccggtggtt 660
ttcttctact tgagccagga cagccgcccg cggagctggt gtctccgcac ggtctgtaac 720
ccgtggttcg agcgagtcag tatgctggtc attcttctca actgtgtgac tctgggtatg 780
ttcaggccgt gtgaggacat tgcctgtgac tcccagcgct gccggatcct gcaggccttc 840
gatgacttca tctttgcctt ctttgctgtg gaaatggtgg tgaagatggt ggccttgggc 900
atctttggga agaaatgtta cctgggagac acttggaacc ggcttgactt tttcattgtc 960
attgcaggga tgctggagta ttcgctggac ctgcagaacg tcagcttctc cgcagtcagg 1020
acagtccgtg tgctgcgacc gctcagggcc attaaccggg tgcccagcat gcgcattctc 1080
gtcacattac tgctggacac cttgcctatg ctgggcaacg tcctgctgct ctgtttcttc 1140
gtctttttca tctttggcat cgtgggcgtc cagctgtggg caggactgct tcgcaaccgg 1200
tgcttcctcc ccgagaactt cagcctcccc ctgagcgtgg acctggagcc ttattaccag 1260
acagagaatg aggacgagag ccccttcatc tgctctcagc ctcgggagaa tggcatgaga 1320
tcctgcagga gtgtgcccac actgcgtggg gaaggcggtg gtggcccacc ctgcagtctg 1380
gactatgaga cctataacag ttccagcaac accacctgtg tcaactggaa ccagtactat 1440
accaactgct ctgcgggcga gcacaacccc ttcaaaggcg ccatcaactt tgacaacatt 1500
ggctatgcct ggatcgccat cttccaggtc atcacactgg agggctgggt cgacatcatg 1560
tacttcgtaa tggacgctca ctccttctac aacttcatct acttcattct tctcatcatc 1620
gtgggctcct tcttcatgat caacctgtgc ctggtggtga ttgccacgca gttctccgag 1680
accaaacagc gggagagtca gctgatgcgg gagcagcgtg tacgattcct gtccaatgct 1740
agcaccctgg caagcttctc tgagccaggc agctgctatg aggagctact caagtacctg 1800
gtgtacatcc tccgaaaagc agcccgaagg ctggcccagg tctctagggc tataggcgtg 1860
cgggctgggc tgctcagcag cccagtggcc cgtagtgggc aggagcccca gcccagtggc 1920
agctgcactc gctcacaccg tcgtctgtct gtccaccacc tggtccacca ccatcaccac 1980
caccatcacc actaccacct gggtaatggg acgctcagag ttccccgggc cagcccagag 2040
atccaggaca gggatgccaa tgggtctcgc cggctcatgc taccaccacc ctctacaccc 2100
actccctctg ggggccctcc gaggggtgcg gagtctgtac acagcttcta ccatgctgac 2160
tgccacttgg agccagtccg ttgccaggca ccccctccca gatgcccatc ggaggcatct 2220
ggtaggactg tgggtagtgg gaaggtgtac cccactgtgc ataccagccc tccaccagag 2280
atactgaagg ataaagcact agtggaggtg gcccccagcc ctgggccccc caccctcacc 2340
agcttcaaca tcccacctgg gcccttcagc tccatgcaca agctcctgga gacacagagt 2400
acgggagcct gccatagctc ctgcaaaatc tccagccctt gctccaaggc agacagtgga 2460
gcctgcgggc cggacagttg tccctactgt gcccggacag gagcaggaga gccagagtcc 2520
gctgaccatg tcatgcctga ctcagacagc gaggctgtgt atgagttcac acaggacgct 2580
cagcacagtg acctccggga tccccacagc cggcggcgac agcggagcct gggcccagat 2640
gcagagccta gttctgtgct ggctttctgg aggctgatct gtgacacatt ccggaagatc 2700
gtagatagca aatactttgg ccggggaatc atgatcgcca tcctggtcaa tacactcagc 2760
atgggcatcg agtaccacga gcagcccgag gagctcacca acgccctgga aatcagcaac 2820
atcgtcttca ccagcctctt cgccttggag atgctgctga aactgcttgt ctacggtccc 2880

tttggctaca ttaagaatcc ctacaacatc tttgatggtg tcattgtggt catcagtgtg 2940
tgggagattg tgggccagca gggaggtggc ctgtcggtgc tgcggacctt ccgcctgatg 3000
cgggtgctga agctggtgcg cttcctgccg gccctgcagc gccagctcgt ggtgctcatg 3060
aagaccatgg acaacgtggc caccttctgc atgctcctca tgctgttcat cttcatcttc 3120
agcatcctgg gcatgcatct ctttggttgc aagttcgcat ctgaacggga tggggacacg 3180
ttgccagacc ggaagaattt cgactccctg ctctgggcca tcgtcactgt ctttcagatt 3240
ctgactcagg aagactggaa taaagtcctc tacaacggca tggcctccac atcgtcttgg 3300
gctgctcttt acttcatcgc cctcatgact tttggcaact atgtgctctt taacctgctg 3360
gtggccattc ttgtggaagg attccaggca gagggagatg ccaccaagtc tgagtcagag 3420
cctgatttct tttcgcccag tgtggatggt gatggggaca gaaagaagcg cttggccctg 3480
gtggctttgg gagaacacgc ggaactacga aagagccttt tgccaccct catcatccat 3540
acggctgcga caccaatgtc acaccccaag agctccagca caggtgtggg ggaagcactg 3600
ggctctggct ctcgacgtac cagtagcagt gggtccgctg agcctggagc tgcccaccat 3660
gagatgaaat gtccgccaag tgcccgcagc tccccgcaca gtccctggag tgcggcaagc 3720
agctggacca gcaggcgctc cagcaggaac agcctgggcc gggcccccag cctaaagcgg 3780
aggagcccga gcggggagcg gaggtccctg ctgtctggag agggccagga gagtcaggat 3840
gaggaggaaa gttcagaaga ggaccgggcc agcccagcag gcagtgacca tcgccacagg 3900
ggttccttgg aacgtgaggc caagagttcc tttgacctgc ctgacactct gcaggtgccg 3960
gggctgcacc gcacagccag cggccggagc tctgcctctg agcaccaaga ctgtaatggc 4020
aagtcggctt cagggcgttt ggcccgcacc ctgaggactg atgaccccca actggatggg 4080
gatgatgaca atgatgaggg aaatctgagc aaaggggaac gcatacaagc ctgggtcaga 4140
tcccggcttc ctgcctgttg ccgagagcga gattcctggt cggcctatat ctttcctcct 4200
cagtcaaggt ttcgtctcct gtgtcaccgg atcatcaccc acaagatgtt tgaccatgtg 4260
gtcctcgtca tcatcttcct caactgtatc accatcgcta tggagcgccc caaaattgac 4320
ccccacagcg ctgagcgcat cttcctgacc ctctccaact acatcttcac ggcagtcttt 4380
ctagctgaaa tgacagtgaa ggtggtggca ctgggctggt gctttgggga gcaggcctac 4440
ctgcgcagca gctggaatgt gctggacggc ttgctggtgc tcatctccgt catcgacatc 4500
ctggtctcca tggtctccga cagcggcacc aagatccttg gcatgctgag ggtgctgcgg 4560
ctgctgcgga ccctgcgtcc actcagggtc atcagccggg cccagggact gaagctggtg 4620
gtagagactc tgatgtcatc cctcaaaccc attggcaaca ttgtggtcat ttgctgtgcc 4680
ttcttcatca tttttggaat tctcggggtg cagctcttca aagggaagtt cttcgtgtgt 4740
cagggtgagg acaccaggaa catcactaac aaatccgact gcgctgaggc cagctaccga 4800
tgggtccggc acaagtacaa ctttgacaac ctgggccagg ctctgatgtc cctgtttgtg 4860
ctggcctcca aggatggttg ggttgacatc atgtatgatg ggctggatgc tgtgggtgtg 4920
gatcagcagc ccatcatgaa ccacaacccc tggatgctgc tatacttcat ctccttcctc 4980
ctcatcgtgg ccttctttgt cctgaacatg tttgtgggcg tggtggtgga gaacttccat 5040
aagtgcagac agcaccagga ggaggaggag gcgaggcggc gtgaggagaa gcgactacgg 5100
aggctggaga aaaagagaag gagtaaggag aagcagatgg ccgaagccca gtgcaagccc 5160
tactactctg actactcgag attccggctc cttgtccacc acctgtgtac cagccactac 5220
ctggacctct tcatcactgg tgtcatcggg ctgaacgtgg tcactatggc catggaacat 5280
taccagcagc cccagatcct ggacgaggct ctgaagatct gcaattacat ctttaccgtc 5340
atctttgtct ttgagtcagt tttcaaactt gtggcctttg cgttccgccg tttcttccag 5400
gacaggtgga accagctgga cctggctatt gtgcttctgt ccatcatggg catcacactg 5460
gaggagattg aggtcaatct gtcgctgccc atcaacccca ccatcatccg tatcatgagg 5520
gtgctccgca ttgctcgagt tctgaagctg ttgaagatgg ctgtgggcat gcgggcactg 5580
ctgcacacgg tgatgcaggc cctgccccag gtggggaacc tgggacttct cttcatgtta 5640
ttgtttttca tctttgcagc tctgggcgtg gagctctttg gagacctgga gtgtgatgag 5700
acacaccctt gtgagggctt gggtcggcat gccaccttta ggaactttgg tatggccttt 5760

ctgaccctct tccgagtctc cactggtgac aactggaatg gtattatgaa ggacccttcc 5820
cgggactgtg accaggagtc cacctgctac aacactgtca tctcccctat ctactttgtg 5880
tccttcgtgc tgacggccca gtttgtgctg gtcaacgtgg tcatagctgt gctgatgaag 5940
cacctggaag aaagcaacaa agaggccaag gaggaggccg agctcgaggc cgagctggag 6000
ctggagatga agacgctcag cccgcagccc cactccccgc tgggcagccc cttcctctgg 6060
cccggggtgg agggtgtcaa cagtactgac agccctaagc ctggggctcc acacaccact 6120
gcccacattg gagcagcctc gggcttctcc cttgagcacc ccacgatggt accccacccc 6180
gaggaggtgc cagtcccccc aggaccagac ctgctgactg tgaggaagtc tggtgtcagc 6240
cggacgcact ctctgcccaa tgacagctac atgtgccgca atgggagcac tgctgagaga 6300
tccctaggac acaggggctg ggggctcccc aaagcccagt caggctccat cttgtccgtt 6360
cactcccaac cagcagacac cagctgcatc ctacagcttc ccaaagatgt gcactatctg 6420
ctccagcctc atggggctcc cacctggggc gccatcccta aactaccccc acctggccgc 6480
tcccctctgg ctcagaggcc tctcaggcgc caggcagcaa taaggactga ctccctggat 6540
gtgcagggcc tgggtagccg ggaagacctg ttgtcagagg tgagtgggcc ctcctgccct 6600
ctgacccggt cctcatcctt ctggggcggg tcgagcatcc aggtgcagca gcgttccggc 6660
atccagagca aagtctccaa gcacatccgc ctgccagccc cttgcccagg cctggaaccc 6720
agctgggcca aggaccctcc agagaccaga agcagcttag agctggacac ggagctgagc 6780
tggatttcag gagacctcct tcccagcagc caggaagaac ccctgttccc acgggacctg 6840
aagaagtgct acagtgtaga gacccagagc tgcaggcgca ggcctgggtt ctggctagat 6900
gaacagcgga gacactccat tgctgtcagc tgtctggaca gcggctccca accccgccta 6960
tgtccaagcc cctcaagcct cgggggccaa cctcttgggg gtcctgggag ccggcctaag 7020
aaaaaactca gcccacccag tatctctata gacccccggg agagccaggg ctctcggccc 7080
ccatgcagtc ctggtgtctg cctcaggagg agggcgccgg ccagtgactc taaggatccc 7140
tcggtctcca gccccccttga cagcacggct gcctcaccct ccccaaagaa agacacgctg 7200
agtctctctg gtttgtcttc tgacccaaca gacatggacc cctgagtcct acccactctc 7260
ccccatcacc tttctccacc gggtgcagat cctacgtccg cctcctgggc agcgtttctg 7320
aaaagtccca cgtaagcagc aagcagccac gaggcacctc acctgccttc ttcagtggct 7380
ggtggggatg acgagcagaa cttccggaga gtcgatctga agagaacaca gccctggagc 7440
ccctgcctcc gggaagaagg aaaaggagaa gcccagtgtg gccaaggctc ccgacaccag 7500
gagctgttgg gagaagcaat acgtttgtgc agaatctcta 7540

<210> 24
<211> 2287
<212> PRT
<213> rat

<400> 24
Met Leu Pro His Arg Val Pro Arg Cys Val Arg Thr Pro Pro Leu Arg
1 5 10 15

Gly Ser Ala Arg Pro Ser Ser Asp Pro Pro Gly Pro Arg Leu Ala Arg
20 25 30

Gly Trp Thr Arg Arg Arg Met Glu Arg Ala Pro Arg Ser Arg Asp Ser
35 40 45

Pro Val Ala Ser Arg Ser Ser Thr Thr Cys Pro Gly Pro Gly Ala Ala
50 55 60

Gly Ala Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala
65 70 75 80

Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu
85 90 95

Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
100 105 110

Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val
115 120 125

Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln
130 135 140

Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe
145 150 155 160

Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys
165 170 175

Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val
180 185 190

Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe
195 200 205

Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn
210 215 220

Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu
225 230 235 240

Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile
245 250 255

Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg
260 265 270

Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu
275 280 285

Pro Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser
290 295 300

Gln Pro Arg Glu Asn Gly Met Arg Ser Cys Arg Ser Val Pro Thr Leu
305 310 315 320

```
Arg Gly Glu Gly Gly Gly Gly Pro Pro Cys Ser Leu Asp Tyr Glu Thr
                325                 330                 335

Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr
            340                 345                 350

Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn
        355                 360                 365

Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr
    370                 375                 380

Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser
385                 390                 395                 400

Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe
                405                 410                 415

Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu
            420                 425                 430

Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe
        435                 440                 445

Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys
    450                 455                 460

Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala
465                 470                 475                 480

Arg Arg Leu Ala Gln Val Ser Arg Ala Ile Gly Val Arg Ala Gly Leu
                485                 490                 495

Leu Ser Ser Pro Val Ala Arg Ser Gly Gln Glu Pro Gln Pro Ser Gly
            500                 505                 510

Ser Cys Thr Arg Ser His Arg Arg Leu Ser Val His His Leu Val His
        515                 520                 525

His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu
    530                 535                 540

Arg Val Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly
545                 550                 555                 560

Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Thr Pro Ser Gly
                565                 570                 575
```

Gly Pro Pro Arg Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp
580 585 590

Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Cys Pro
595 600 605

Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr
610 615 620

Val His Thr Ser Pro Pro Pro Glu Ile Leu Lys Asp Lys Ala Leu Val
625 630 635 640

Glu Val Ala Pro Ser Pro Gly Pro Pro Thr Leu Thr Ser Phe Asn Ile
645 650 655

Pro Pro Gly Pro Phe Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser
660 665 670

Thr Gly Ala Cys His Ser Ser Cys Lys Ile Ser Ser Pro Cys Ser Lys
675 680 685

Ala Asp Ser Gly Ala Cys Gly Pro Asp Ser Cys Pro Tyr Cys Ala Arg
690 695 700

Thr Gly Ala Gly Glu Pro Glu Ser Ala Asp His Val Met Pro Asp Ser
705 710 715 720

Asp Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp
725 730 735

Leu Arg Asp Pro His Ser Arg Arg Arg Gln Arg Ser Leu Gly Pro Asp
740 745 750

Ala Glu Pro Ser Ser Val Leu Ala Phe Trp Arg Leu Ile Cys Asp Thr
755 760 765

Phe Arg Lys Ile Val Asp Ser Lys Tyr Phe Gly Arg Gly Ile Met Ile
770 775 780

Ala Ile Leu Val Asn Thr Leu Ser Met Gly Ile Glu Tyr His Glu Gln
785 790 795 800

Pro Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr
805 810 815

Ser Leu Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Val Tyr Gly Pro
820 825 830

Phe Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val
835 840 845

Val Ile Ser Val Trp Glu Ile Val Gly Gln Gln Gly Gly Gly Leu Ser
850 855 860

Val Leu Arg Thr Phe Arg Leu Met Arg Val Leu Lys Leu Val Arg Phe
865 870 875 880

Leu Pro Ala Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp
885 890 895

Asn Val Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe
900 905 910

Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg
915 920 925

Asp Gly Asp Thr Leu Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp
930 935 940

Ala Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Lys
945 950 955 960

Val Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr
965 970 975

Phe Ile Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu
980 985 990

Val Ala Ile Leu Val Glu Gly Phe Gln Ala Glu Gly Asp Ala Thr Lys
995 1000 1005

Ser Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Val Asp Gly Asp Gly
1010 1015 1020

Asp Arg Lys Lys Arg Leu Ala Leu Val Ala Leu Gly Glu His Ala Glu
1025 1030 1035 1040

Leu Arg Lys Ser Leu Leu Pro Pro Leu Ile Ile His Thr Ala Ala Thr
1045 1050 1055

Pro Met Ser His Pro Lys Ser Ser Ser Thr Gly Val Gly Glu Ala Leu
1060 1065 1070

Gly Ser Gly Ser Arg Arg Thr Ser Ser Ser Gly Ser Ala Glu Pro Gly
1075 1080 1085

Ala Ala His His Glu Met Lys Cys Pro Pro Ser Ala Arg Ser Ser Pro
1090 1095 1100

His Ser Pro Trp Ser Ala Ala Ser Ser Trp Thr Ser Arg Arg Ser Ser
1105 1110 1115 1120

Arg Asn Ser Leu Gly Arg Ala Pro Ser Leu Lys Arg Arg Ser Pro Ser
1125 1130 1135

Gly Glu Arg Arg Ser Leu Leu Ser Gly Glu Gly Gln Glu Ser Gln Asp
1140 1145 1150

Glu Glu Glu Ser Ser Glu Glu Asp Arg Ala Ser Pro Ala Gly Ser Asp
1155 1160 1165

His Arg His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp
1170 1175 1180

Leu Pro Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly
1185 1190 1195 1200

Arg Ser Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser
1205 1210 1215

Gly Arg Leu Ala Arg Thr Leu Arg Thr Asp Asp Pro Gln Leu Asp Gly
1220 1225 1230

Asp Asp Asp Asn Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Ile Gln
1235 1240 1245

Ala Trp Val Arg Ser Arg Leu Pro Ala Cys Cys Arg Glu Arg Asp Ser
1250 1255 1260

Trp Ser Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys
1265 1270 1275 1280

His Arg Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile
1285 1290 1295

Ile Phe Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp
1300 1305 1310

Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe
1315 1320 1325

Thr Ala Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly
1330 1335 1340

Trp Cys Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu
1345 1350 1355 1360

Asp Gly Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met
1365 1370 1375

Val Ser Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg
1380 1385 1390

Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly
1395 1400 1405

Leu Lys Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly
1410 1415 1420

Asn Ile Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu
1425 1430 1435 1440

Gly Val Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp
1445 1450 1455

Thr Arg Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg
1460 1465 1470

Trp Val Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met
1475 1480 1485

Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr
1490 1495 1500

Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His
1505 1510 1515 1520

Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala
1525 1530 1535

Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His
1540 1545 1550

Lys Cys Arg Gln His Gln Glu Glu Glu Glu Ala Arg Arg Arg Glu Glu
1555 1560 1565

Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Ser Lys Glu Lys Gln
1570 1575 1580

Met Ala Glu Ala Gln Cys Lys Pro Tyr Tyr Ser Asp Tyr Ser Arg Phe
1585 1590 1595 1600

Arg Leu Leu Val His His Leu Cys Thr Ser His Tyr Leu Asp Leu Phe
1605 1610 1615

Ile Thr Gly Val Ile Gly Leu Asn Val Val Thr Met Ala Met Glu His
1620 1625 1630

Tyr Gln Gln Pro Gln Ile Leu Asp Glu Ala Leu Lys Ile Cys Asn Tyr
1635 1640 1645

Ile Phe Thr Val Ile Phe Val Phe Glu Ser Val Phe Lys Leu Val Ala
1650 1655 1660

Phe Ala Phe Arg Arg Phe Phe Gln Asp Arg Trp Asn Gln Leu Asp Leu
1665 1670 1675 1680

Ala Ile Val Leu Leu Ser Ile Met Gly Ile Thr Leu Glu Glu Ile Glu
1685 1690 1695

Val Asn Leu Ser Leu Pro Ile Asn Pro Thr Ile Ile Arg Ile Met Arg
1700 1705 1710

Val Leu Arg Ile Ala Arg Val Leu Lys Leu Leu Lys Met Ala Val Gly
1715 1720 1725

Met Arg Ala Leu Leu His Thr Val Met Gln Ala Leu Pro Gln Val Gly
1730 1735 1740

Asn Leu Gly Leu Leu Phe Met Leu Leu Phe Phe Ile Phe Ala Ala Leu
1745 1750 1755 1760

Gly Val Glu Leu Phe Gly Asp Leu Glu Cys Asp Glu Thr His Pro Cys
1765 1770 1775

Glu Gly Leu Gly Arg His Ala Thr Phe Arg Asn Phe Gly Met Ala Phe
1780 1785 1790

Leu Thr Leu Phe Arg Val Ser Thr Gly Asp Asn Trp Asn Gly Ile Met
1795 1800 1805

Lys Asp Pro Ser Arg Asp Cys Asp Gln Glu Ser Thr Cys Tyr Asn Thr
1810 1815 1820

Val Ile Ser Pro Ile Tyr Phe Val Ser Phe Val Leu Thr Ala Gln Phe
1825 1830 1835 1840

Val Leu Val Asn Val Val Ile Ala Val Leu Met Lys His Leu Glu Glu
1845 1850 1855

Ser Asn Lys Glu Ala Lys Glu Glu Ala Glu Leu Glu Ala Glu Leu Glu
1860 1865 1870

Leu Glu Met Lys Thr Leu Ser Pro Gln Pro His Ser Pro Leu Gly Ser
1875 1880 1885

Pro Phe Leu Trp Pro Gly Val Glu Gly Val Asn Ser Thr Asp Ser Pro
1890 1895 1900

Lys Pro Gly Ala Pro His Thr Thr Ala His Ile Gly Ala Ala Ser Gly
1905 1910 1915 1920

Phe Ser Leu Glu His Pro Thr Met Val Pro His Pro Glu Glu Val Pro
1925 1930 1935

Val Pro Leu Gly Pro Asp Leu Leu Thr Val Arg Lys Ser Gly Val Ser
1940 1945 1950

Arg Thr His Ser Leu Pro Asn Asp Ser Tyr Met Cys Arg Asn Gly Ser
1955 1960 1965

Thr Ala Glu Arg Ser Leu Gly His Arg Gly Trp Gly Leu Pro Lys Ala
1970 1975 1980

Gln Ser Gly Ser Ile Leu Ser Val His Ser Gln Pro Ala Asp Thr Ser
1985 1990 1995 2000

Cys Ile Leu Gln Leu Pro Lys Asp Val His Tyr Leu Leu Gln Pro His
2005 2010 2015

Gly Ala Pro Thr Trp Gly Ala Ile Pro Lys Leu Pro Pro Pro Gly Arg
2020 2025 2030

Ser Pro Leu Ala Gln Arg Pro Leu Arg Arg Gln Ala Ala Ile Arg Thr
2035 2040 2045

Asp Ser Leu Asp Val Gln Gly Leu Gly Ser Arg Glu Asp Leu Leu Ser
2050 2055 2060

Glu Val Ser Gly Pro Ser Cys Pro Leu Thr Arg Ser Ser Ser Phe Trp
2065 2070 2075 2080

Gly Gly Ser Ser Ile Gln Val Gln Gln Arg Ser Gly Ile Gln Ser Lys
2085 2090 2095

Val Ser Lys His Ile Arg Leu Pro Ala Pro Cys Pro Gly Leu Glu Pro
2100 2105 2110

Ser Trp Ala Lys Asp Pro Pro Glu Thr Arg Ser Ser Leu Glu Leu Asp
2115 2120 2125

Thr Glu Leu Ser Trp Ile Ser Gly Asp Leu Leu Pro Ser Ser Gln Glu
2130 2135 2140

Glu Pro Leu Phe Pro Arg Asp Leu Lys Lys Cys Tyr Ser Val Glu Thr
2145 2150 2155 2160

Gln Ser Cys Arg Arg Arg Pro Gly Phe Trp Leu Asp Glu Gln Arg Arg
2165 2170 2175

His Ser Ile Ala Val Ser Cys Leu Asp Ser Gly Ser Gln Pro Arg Leu
2180 2185 2190

Cys Pro Ser Pro Ser Ser Leu Gly Gly Gln Pro Leu Gly Gly Pro Gly
2195 2200 2205

Ser Arg Pro Lys Lys Lys Leu Ser Pro Pro Ser Ile Ser Ile Asp Pro
2210 2215 2220

Pro Glu Ser Gln Gly Ser Arg Pro Pro Cys Ser Pro Gly Val Cys Leu
2225 2230 2235 2240

Arg Arg Arg Ala Pro Ala Ser Asp Ser Lys Asp Pro Ser Val Ser Ser
2245 2250 2255

Pro Leu Asp Ser Thr Ala Ala Ser Pro Ser Pro Lys Lys Asp Thr Leu
2260 2265 2270

Ser Leu Ser Gly Leu Ser Ser Asp Pro Thr Asp Met Asp Pro Glx
2275 2280 2285

<210> 25
<211> 8447
<212> DNA
<213> rat

<400> 25
cgggataatt ctgtctcatt accataggca cacaataaaa catctttacc atttctctaa 60
actcagccat tggccaaagc cagaaggaag acctgtgcat ttgcatctgg ggatccgatc 120
ctgactgatg ctctaggttg ctgcgtatac agtggaggag actgtgagaa aggaccatag 180
tagtcaagga agaaagcatc ctgggacaga gccacaatca cgagatgatt cctaccaatg 240
aacctcttcg gactgggtcc cagtgacagc gccgcccggg ctatgccacg gggacgccgc 300
tagccaccgg agcgaggtga gatgcggagg gtacgcgcgc ttactgcgcg cctgggaccc 360
tttgaacttg agctctgtgg gctccgagcc cctagggctc ccgcaaccct tcgcctcggc 420

cttgggggtg gggctgccag gctttgccgg cgggaggggg cgggggcgc atttgtctct 480
aataaggaga gacaaagaca tcccggcggc cgcggctgtt cccgcagctc cgctccgcct 540
gaggcggggc gggggcgtcg ttcctgggcc agggtcacct cctgccctct ctccgcaggt 600
gctgccctcc gccaccatga ccgagggcac gctggcagcg gacgaagtcc gggtgcccct 660
gggcgcttcg ccgccggccc ctgcagcgcc ggtgagagct tccccagcga gccctggggc 720
gccggggcgc gaggagcagg gaggatccgg gtcgggagtg ttggctcccg agagcccagg 780
gaccgagtgt ggtgcggacc tgggcgccga cgaggaacag ccggtcccat acccagctct 840
ggctgccaca gtcttcttct gcctcgggca aaccacgcgg ccgcgcagct ggtgcctccg 900
actggtttgt aacccgtggt tcgagcacgt cagcatgctg gtcatcatgc tgaactgcgt 960
gacactgggc atgttcaggc cctgtgagga tgttgagtgc cgctccgaac gttgcagcat 1020
cttggaggcc ttcgacgact tcatctttgc cttcttcgcc gtggagatgg tgatcaagat 1080
ggtggctttg gggctgtttg ggcaaaaatg ctacctgggt gacacctgga acaggctgga 1140
cttcttcatt gtcatggcgg gcatgatgga gtactctctg gacggacaca aggtgagcct 1200
ctctgccatc cgaaccgtgc gtgtgctgcg gcccctccgc gccatcaacc gagtccccag 1260
tatgcggatc ctggtcactc tgctgctgga cacgctgccc atgcttggga atgtcctcct 1320
cctctgcttc ttcgtcttct tcatcttcgg cattgttggg gtccagctct gggctggcct 1380
gcttcggaac cgatgcttcc tggacagcgc cttcgtcagg aacaacaacc tgaccttctt 1440
gcggccatac taccagacgg aggagggtga ggagaaccct ttcatctgct cctcccgccg 1500
tgacaacggc atgcagaagt gctcgcacat ccccagccgc cgtgagcttc gagtgcagtg 1560
cacactcggc tgggaggcct atgggcagcc acaggctgag gatgggggtg ctggccgcaa 1620
cgcctgtatc aactggaacc agtattacaa cgtgtgccgc tcgggggaat tcaaccctca 1680
caacggtgcc atcaacttcg acaacattgg ctacgcttgg attgccatct tccaggtcat 1740
cacactggag ggctgggtgg acatcatgta ctacgtcatg gatgcccact cgttctacaa 1800
cttcatctac ttcatcctcc tcatcattat gggctccttc ttcatgatca acctgtgcct 1860
ggtggtgata gccacacagt tctcagagac aaagcaaagg gaaaaccagc tgatgcgaga 1920
acagcgggcc cgctatctgt ccaacgacag cactctggcc agcttctcag agcccggcag 1980
ctgctacgag gagctcctca agtatgtagg ccacatcttc cggaaggtta aacgccgtag 2040
cctgcgtctt tatgcccgct ggcagagccg ctggcgtaag aaggtggatc ccagcagtac 2100
cgtgcatggc caaggccctg ggcggcggcc acgacgggca ggcaggcgta cagcttcagt 2160
gcaccatctg gtctaccacc accaccacca ccatcaccac cattaccact ttagccacgg 2220
tggcccacgc aggcccagcc cagagccagg tgctggtgac aacaggttgg tcagggcctg 2280
tgcgccaccc tcgccgccat ccccaggcca tgggccacca gactctgagt ctgtgcacag 2340
tatctaccat gctgactgcc acgtggaggg gccgcaggaa cgagcccgag tggcacactc 2400
catagccact gctgctagcc tcaagctggc ctcaggtttg ggtaccatga actaccccac 2460
catcctacct tcaggaacag tcaacagcaa aggtggcacc agctcacgac ccaaggggct 2520
acgaggtgct ggcgccccag gggctgcagt acacagccct ctgagcctgg gaagccccag 2580
accctatgag aagatccagg atgtggtggg agaacaagga ctaggccgag cctctagcca 2640
cctgtcaggc ctgagtgtgc cttgcccccc gcccagcccc caggctggca cgctgacctg 2700
tgagctgaag agctgcccat attgtgccag cgccctggag gaccccgagt ttgaattcag 2760
tggctcagag agcggggact cggatgccca cggagtctat gagtttaccc aggatgtacg 2820
gcatggggat tgtcgggacc ctgtgcagca gccccatgaa gtgggcacac caggccacag 2880
caatgagcgg cggcggacac cactgcggaa ggcctcacaa ccaggaggga taggccacct 2940
ctgggcatcc ttcagtggca agctacgtcg cattgtagac agcaagtact tcaaccgagg 3000
catcatggca gccatcctcg tcaatactct gagcatgggc gttgagtatc atgaacagcc 3060
tgaggagctg accaacgccc tggagataag caacatcgtg ttcaccagca tgtttgcctt 3120
ggagatgcta ctgaagctgc tggcctgcgg cccactggga tacatccgga acccctacaa 3180
catcttcgat ggcattgttg tcgtcataag tgtctgggag atcgtggggc aggcagacgg 3240
tggccagtct gtgctgcgca ccttcaggct gctgcgggtg ctgaagctgg tgcgcttcct 3300

gccggccctg cggcgccagc tcgtggtgct catgaggacc atggacaacg tggccacctt 3360
ctgcatgctc ctcatgctgt tcatcttcat cttcagcatc ctgggcatgc acctgttcgg 3420
ctgtaagttc agcctgaaga cagactctgg agacaccgtc cctgacagga agaacttcga 3480
ctccctactg tgggccatcg tcaccgtgtt tcagatcttg acacaggaag actggaacgt 3540
ggttctgtac aacggcatgg cctccacttc gtcctgggcc gccctttact ttgtggccct 3600
catgaccttt gggaactatg tgctcttcaa cctgctggta gccatcctgg tggaaggttt 3660
ccaggcagag ggtgacgcca ccagatctga caccgacgag gataagacgt ctacccagct 3720
agagggagat ttcgataagc tcagagatct tcgagccaca gagatgaaga tgtattcact 3780
ggcagtgacc cctaacgggc acctagaggg ccgaggcagc ctgccgccgc ccctcatcac 3840
tcacacggca gctacgccta tgcctactcc caaaagctcc ccaaacctgg acgtggccca 3900
tgctctcctg gactctcggc gcagcagcag cggctctgtg gacccccagc tgggggacca 3960
gaagtctctg gccagcctcc gcagctcccc ttgcacccca tggggcccca acagcgctgg 4020
gagcagcagg cgctccagtt ggaacagcct gggccgcgca cccagcctca aacgccgcag 4080
ccagtgtggg gagcgcgagt ccctgctctc tggagagggg aagggcagca ccgatgacga 4140
ggccgaggac agcagaccaa gcacgggaac ccacccaggg gcctcgccag ggccccgagc 4200
cacgccactg cggcgtgccg agtcattgga ccaccgcagc acgctggacc tgtgtccacc 4260
acggcctgcg cctcctgccg tccaagttca tgactgcaac gggcagatgg tggccctgcc 4320
cagcgagttc tttctgcgca tcgacagcca caaggaggat gcagcggagt ttgatgatga 4380
catagaggat agctgctgct tccgtctaca caaagtgctg gaaccctatg caccccagtg 4440
gtgccgtagc cgggagtcct gggccctgta tctcttccca ccgcagaaca ggctacgcgt 4500
ctcctgccag aaagtcatcg cacacaagat gtttgaccac gtggtccttg tcttcatctt 4560
cctcaactgt atcaccattg ctctggagag gccagacatt gacccaggca gcactgagcg 4620
ggccttcctc agcgtctcca actacatctt cacagccatc ttcgtggtgg agatgatggt 4680
gaaggtggta gccctgggac tgctgtgggg tgaacatgcc tacctacaga gcagttggaa 4740
tgtgctggac gggctgcttg tcctggtatc cctggttgac atcatcgtgg ccatggcctc 4800
agctggcggt gccaagatcc taggcgtcct gcgtgtcgtg cgcctgctgc ggaccctgag 4860
gcctctgagg gtcatcagcc gagctccagg cctcaagctg gttgtagaga ctctgatatc 4920
atcgctcagg cccattggga acatcgtcct catctgctgc gccttcttca tcatctttgg 4980
catcctcggg gtgcagcttt tcaagggcaa attctactac tgcgagggca cagataccag 5040
gaatatcacc accaaggccg agtgccatgc tgcccactac cgctgggtga ggcgcaaata 5100
caactttgac aacctgggtc aggcgctgat gtctctgttc gtgctgtcat ctaaggatgg 5160
ctgggtaaac atcatgtatg acgggctgga tgccgtgggc atcgaccagc agcccgtgca 5220
gaaccacaac ccctggatgc tgctctactt catctccttc ctgctcatcg tcagcttctt 5280
cgtgctcaac atgtttgtgg gcgtggtggt ggagaacttc cacaagtgcc ggcagcacca 5340
ggaggctgag gaggctcggc gccgggagga gaaacggctg cggcgcctgg agaggaggcg 5400
caggaaggcc cagcgccggc cctactacgc agactattca cacactcgcc gctccatcca 5460
ttcgctgtgc accagccact acctggacct cttcatcacc ttcatcatct gcctcaatgt 5520
catcaccatg tccatggagc actacaacca gcccaagtcc ctggatgagg ccctcaagta 5580
ctgcaactac gtctttacca tcgtcttcgt ctttgaggct gcactgaagc tggtggcctt 5640
tgggttccgg aggttcttca aggacaggtg gaaccagctg gacttggcca tcgtcctcct 5700
atccatcatg ggcattgcgc tggaggagat tgagatgaac gccgccctgc ccatcaatcc 5760
caccatcatc cgcatcatgc gtgtgcttcg aatcgcccgt gtgctgaagc tactgaagat 5820
ggccacaggc atgcgcgcct tgctggatac tgtggttcaa gctctgcctc aggtagggaa 5880
ccttggtctt cttttcatgc tcctgttttt tatctatgct gccctgggag tggagctgtt 5940
tgggaggcta gagtgcagcg aggataaccc ctgcgagggc ctgagcaggc acgctacctt 6000
caccaacttc ggcatggcct tcctcacact gttccgagtg tccactgggg acaactggaa 6060
tgggattatg aaggataccc tccgtgagtg tacccgtgag gacaagcact gcctcagcta 6120
cctgcccgcg ctctcacccg tctacttcgt caccttcatg ctggtggctc agttcgtgct 6180

ggtcaatgtg gtggtggccg tgctcatgaa gcacctggag gagagcaaca aggaggcccg 6240
cgaggatgca gagatggacg ccgagatcga gctggagatg gcacaggggt ccacagccca 6300
gcccccacct acagcacagg aaagccaagg tacccagcca gacaccccga acctcctggt 6360
cgtgcgaaaa gtatctgtgt ccaggatgct ctcgctgccc aatgacagct acatgttcag 6420
gccggtggct cccgcggctg ccccacattc ccacccactg caggaagtgg agatggagac 6480
ctacacaggc ccggtcacct ctgctcactc gccacccctg gagccccgcg cctctttcca 6540
ggtcccatca gccgcgtcct ccccagccag ggtcagtgac ccccttttgtg ccctttcacc 6600
ccggggtaca ccccgctctc tgagtctctc acggatactc tgcagacagg aggccatgca 6660
ctctgagtcc ctggaaggga aggttgatga tgttggagga gacagcatcc cagactacac 6720
agagcctgct gaaaatatgt ccacgagcca ggcatcaaca ggtgccccga ggtcccctcc 6780
gtgctccccg cgacctgcca gcgtccgtac ccgcaagcac acgtttgggc aacgctgcat 6840
ctccagccgc cctcccaccc tgggaggaga tgaggctgaa gcagcagacc cagcagatga 6900
ggaggtcagc cacatcacca gctcagccca cccctggccg gctacagagc cccacagccc 6960
tgaggcctcc ccaacagcct ctcctgtgaa aggcacaatg ggcagtgggc gggacccacg 7020
caggttctgc agtgtagatg ctcagagctt cctggacaaa ccaggtcggc cagatgcaca 7080
acggtggtcc tcagtggaac tggataacgg agaaagccac ctagagtccg gggaagtgag 7140
gggccgggcc tcagagctcg aaccagctct tgggtcacga aggaagaaga agatgagccc 7200
tccctgcatc tccattgaac ctcccactaa ggatgagggc tcttcccggc cccctgcagc 7260
cgaaggaggc aacactaccc tgaggcgccg aaccccatcc tgtgaggctg ccctccatag 7320
ggactgccca gagcctacag aaggcccagg caccggaggg gaccctgtag ccaagggtga 7380
gcgctggggc caggcctctt gccgagcaga gcatctgact gtccccaact ttgcctttga 7440
gcctctggac atgggcggac ctggtggaga ctgtttcttg gacagtgacc aaagtgtgac 7500
cccagaaccc agagtttcct ctttgggggc tatagtgcct ctgatactag aaactgaact 7560
ttctatgccc tctcctgact gcccagagaa ggaacaagga ctgtacctca ctgtgcccca 7620
gacccccttg aagaaaccag ggtctacccc agccactcct gccccagatg acagtggaga 7680
tgagcctgtg tagatggggc tgcgtgtcca cagggctttg gcattgaggt tgttggctcc 7740
tgcagggtgg tagggccatg agtggaccct gcttaggccc cactaaggca gagggaccgg 7800
gagataacca tcccaggaga ggcagcagac atcccgtctc tgcaccatga cacaggagca 7860
gcctcgggcc ccacgagcct ccctcgtggt gattcaggtt tgggttttcc tgagttttaa 7920
ccaccaccag aagctgtacc aggaccaggt catcagtctc aggaggagag gctgtgtcct 7980
gggaaggacc agtaattcct cacaggcacc acagctccat ccatgtgaca cacaggtttc 8040
cgacagggag tacagcttga gcctgtgtac attgggtcct gcagccaccg cacccaatat 8100
caccttcgtt cacagtcctg tttctgtcca ccactcggca tccttccctc tcacagtgcc 8160
cctcccccat tccatccccc tagatggtct agaactttgc agtgaccctg ggaagtactg 8220
acccatgcaa taagacattg cagtcccaac tgaggtgggg cttcccatcc attccaggct 8280
gttgggctca acattcattt gacatccatt tgctttatgt catccgtttc tacaaattca 8340
ggttaaatgt tgcaataatc tgatgcagaa aacttggctt cctaagtcaa agctgagggg 8400
aggggagggg aggggcaagg caaatctgaa taaacactaa cttattg 8447

<210> 26
<211> 2359
<212> PRT
<213> rat

<400> 26
Met Thr Glu Gly Thr Leu Ala Ala Asp Glu Val Arg Val Pro Leu Gly
1 5 10 15

```
Ala Ser Pro Pro Ala Pro Ala Ala Pro Val Arg Ala Ser Pro Ala Ser
            20                  25                  30

Pro Gly Ala Pro Gly Arg Glu Glu Gln Gly Gly Ser Gly Ser Gly Val
        35                  40                  45

Leu Ala Pro Glu Ser Pro Gly Thr Glu Cys Gly Ala Asp Leu Gly Ala
    50                  55                  60

Asp Glu Glu Gln Pro Val Pro Tyr Pro Ala Leu Ala Ala Thr Val Phe
65                  70                  75                  80

Phe Cys Leu Gly Gln Thr Thr Arg Pro Arg Ser Trp Cys Leu Arg Leu
                85                  90                  95

Val Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu
            100                 105                 110

Asn Cys Val Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Val Glu Cys
        115                 120                 125

Arg Ser Glu Arg Cys Ser Ile Leu Glu Ala Phe Asp Asp Phe Ile Phe
    130                 135                 140

Ala Phe Phe Ala Val Glu Met Val Ile Lys Met Val Ala Leu Gly Leu
145                 150                 155                 160

Phe Gly Gln Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe
                165                 170                 175

Phe Ile Val Met Ala Gly Met Met Glu Tyr Ser Leu Asp Gly His Lys
            180                 185                 190

Val Ser Leu Ser Ala Ile Arg Thr Val Arg Val Leu Arg Pro Leu Arg
        195                 200                 205

Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu
    210                 215                 220

Asp Thr Leu Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val
225                 230                 235                 240

Phe Phe Ile Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu
                245                 250                 255

Arg Asn Arg Cys Phe Leu Asp Ser Ala Phe Val Arg Asn Asn Asn Leu
            260                 265                 270
```

```
Thr Phe Leu Arg Pro Tyr Tyr Gln Thr Glu Glu Gly Glu Glu Asn Pro
        275                 280                 285

Phe Ile Cys Ser Ser Arg Arg Asp Asn Gly Met Gln Lys Cys Ser His
    290                 295                 300

Ile Pro Ser Arg Arg Glu Leu Arg Val Gln Cys Thr Leu Gly Trp Glu
305                 310                 315                 320

Ala Tyr Gly Gln Pro Gln Ala Glu Asp Gly Gly Ala Gly Arg Asn Ala
                325                 330                 335

Cys Ile Asn Trp Asn Gln Tyr Tyr Asn Val Cys Arg Ser Gly Glu Phe
            340                 345                 350

Asn Pro His Asn Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala Trp
        355                 360                 365

Ile Ala Ile Phe Gln Val Ile Thr Leu Glu Gly Trp Val Asp Ile Met
    370                 375                 380

Tyr Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile
385                 390                 395                 400

Leu Leu Ile Ile Met Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val
                405                 410                 415

Val Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu Asn Gln Leu
            420                 425                 430

Met Arg Glu Gln Arg Ala Arg Tyr Leu Ser Asn Asp Ser Thr Leu Ala
        435                 440                 445

Ser Phe Ser Glu Pro Gly Ser Cys Tyr Glu Glu Leu Leu Lys Tyr Val
    450                 455                 460

Gly His Ile Phe Arg Lys Val Lys Arg Arg Ser Leu Arg Leu Tyr Ala
465                 470                 475                 480

Arg Trp Gln Ser Arg Trp Arg Lys Lys Val Asp Pro Ser Ser Thr Val
                485                 490                 495

His Gly Gln Gly Pro Gly Arg Arg Pro Arg Arg Ala Gly Arg Arg Thr
            500                 505                 510

Ala Ser Val His His Leu Val Tyr His His His His His His His His
        515                 520                 525
```

```
His Tyr His Phe Ser His Gly Gly Pro Arg Arg Pro Ser Pro Glu Pro
    530                 535                 540

Gly Ala Gly Asp Asn Arg Leu Val Arg Ala Cys Ala Pro Pro Ser Pro
545                 550                 555                 560

Pro Ser Pro Gly His Gly Pro Pro Asp Ser Glu Ser Val His Ser Ile
                565                 570                 575

Tyr His Ala Asp Cys His Val Glu Gly Pro Gln Glu Arg Ala Arg Val
            580                 585                 590

Ala His Ser Ile Ala Thr Ala Ala Ser Leu Lys Leu Ala Ser Gly Leu
        595                 600                 605

Gly Thr Met Asn Tyr Pro Thr Ile Leu Pro Ser Gly Thr Val Asn Ser
    610                 615                 620

Lys Gly Gly Thr Ser Ser Arg Pro Lys Gly Leu Arg Gly Ala Gly Ala
625                 630                 635                 640

Pro Gly Ala Ala Val His Ser Pro Leu Ser Leu Gly Ser Pro Arg Pro
                645                 650                 655

Tyr Glu Lys Ile Gln Asp Val Val Gly Glu Gln Gly Leu Gly Arg Ala
            660                 665                 670

Ser Ser His Leu Ser Gly Leu Ser Val Pro Cys Pro Leu Pro Ser Pro
        675                 680                 685

Gln Ala Gly Thr Leu Thr Cys Glu Leu Lys Ser Cys Pro Tyr Cys Ala
    690                 695                 700

Ser Ala Leu Glu Asp Pro Glu Phe Glu Phe Ser Gly Ser Glu Ser Gly
705                 710                 715                 720

Asp Ser Asp Ala His Gly Val Tyr Glu Phe Thr Gln Asp Val Arg His
                725                 730                 735

Gly Asp Cys Arg Asp Pro Val Gln Gln Pro His Glu Val Gly Thr Pro
            740                 745                 750

Gly His Ser Asn Glu Arg Arg Arg Thr Pro Leu Arg Lys Ala Ser Gln
        755                 760                 765

Pro Gly Gly Ile Gly His Leu Trp Ala Ser Phe Ser Gly Lys Leu Arg
    770                 775                 780
```

```
Arg Ile Val Asp Ser Lys Tyr Phe Asn Arg Gly Ile Met Ala Ala Ile
785                 790                 795                 800

Leu Val Asn Thr Leu Ser Met Gly Val Glu Tyr His Glu Gln Pro Glu
                805                 810                 815

Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr Ser Met
            820                 825                 830

Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Ala Cys Gly Pro Leu Gly
        835                 840                 845

Tyr Ile Arg Asn Pro Tyr Asn Ile Phe Asp Gly Ile Val Val Val Ile
    850                 855                 860

Ser Val Trp Glu Ile Val Gly Gln Ala Asp Gly Gly Gln Ser Val Leu
865                 870                 875                 880

Arg Thr Phe Arg Leu Leu Arg Val Leu Lys Leu Val Arg Phe Leu Pro
                885                 890                 895

Ala Leu Arg Arg Gln Leu Val Val Leu Met Arg Thr Met Asp Asn Val
            900                 905                 910

Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe Ser Ile
        915                 920                 925

Leu Gly Met His Leu Phe Gly Cys Lys Phe Ser Leu Lys Thr Asp Ser
    930                 935                 940

Gly Asp Thr Val Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp Ala
945                 950                 955                 960

Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Val Val
                965                 970                 975

Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr Phe
            980                 985                 990

Val Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu Val
        995                1000                1005

Ala Ile Leu Val Glu Gly Phe Gln Ala Glu Gly Asp Ala Thr Arg Ser
   1010                1015                1020

Asp Thr Asp Glu Asp Lys Thr Ser Thr Gln Leu Glu Gly Asp Phe Asp
1025                1030                1035                1040
```

Lys Leu Arg Asp Leu Arg Ala Thr Glu Met Lys Met Tyr Ser Leu Ala
1045 1050 1055

Val Thr Pro Asn Gly His Leu Glu Gly Arg Gly Ser Leu Pro Pro Pro
1060 1065 1070

Leu Ile Thr His Thr Ala Ala Thr Pro Met Pro Thr Pro Lys Ser Ser
1075 1080 1085

Pro Asn Leu Asp Val Ala His Ala Leu Leu Asp Ser Arg Arg Ser Ser
1090 1095 1100

Ser Gly Ser Val Asp Pro Gln Leu Gly Asp Gln Lys Ser Leu Ala Ser
1105 1110 1115 1120

Leu Arg Ser Ser Pro Cys Thr Pro Trp Gly Pro Asn Ser Ala Gly Ser
1125 1130 1135

Ser Arg Arg Ser Ser Trp Asn Ser Leu Gly Arg Ala Pro Ser Leu Lys
1140 1145 1150

Arg Arg Ser Gln Cys Gly Glu Arg Glu Ser Leu Leu Ser Gly Glu Gly
1155 1160 1165

Lys Gly Ser Thr Asp Asp Glu Ala Glu Asp Ser Arg Pro Ser Thr Gly
1170 1175 1180

Thr His Pro Gly Ala Ser Pro Gly Pro Arg Ala Thr Pro Leu Arg Arg
1185 1190 1195 1200

Ala Glu Ser Leu Asp His Arg Ser Thr Leu Asp Leu Cys Pro Pro Arg
1205 1210 1215

Pro Ala Pro Pro Ala Val Gln Val His Asp Cys Asn Gly Gln Met Val
1220 1225 1230

Ala Leu Pro Ser Glu Phe Phe Leu Arg Ile Asp Ser His Lys Glu Asp
1235 1240 1245

Ala Ala Glu Phe Asp Asp Asp Ile Glu Asp Ser Cys Cys Phe Arg Leu
1250 1255 1260

His Lys Val Leu Glu Pro Tyr Ala Pro Gln Trp Cys Arg Ser Arg Glu
1265 1270 1275 1280

Ser Trp Ala Leu Tyr Leu Phe Pro Pro Gln Asn Arg Leu Arg Val Ser
1285 1290 1295

Cys Gln Lys Val Ile Ala His Lys Met Phe Asp His Val Val Leu Val
1300 1305 1310

Phe Ile Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro Asp Ile
1315 1320 1325

Asp Pro Gly Ser Thr Glu Arg Ala Phe Leu Ser Val Ser Asn Tyr Ile
1330 1335 1340

Phe Thr Ala Ile Phe Val Val Glu Met Met Val Lys Val Val Ala Leu
1345 1350 1355 1360

Gly Leu Leu Trp Gly Glu His Ala Tyr Leu Gln Ser Ser Trp Asn Val
1365 1370 1375

Leu Asp Gly Leu Leu Val Leu Val Ser Leu Val Asp Ile Ile Val Ala
1380 1385 1390

Met Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg Val Val
1395 1400 1405

Arg Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Pro
1410 1415 1420

Gly Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Arg Pro Ile
1425 1430 1435 1440

Gly Asn Ile Val Leu Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile
1445 1450 1455

Leu Gly Val Gln Leu Phe Lys Gly Lys Phe Tyr Tyr Cys Glu Gly Thr
1460 1465 1470

Asp Thr Arg Asn Ile Thr Thr Lys Ala Glu Cys His Ala Ala His Tyr
1475 1480 1485

Arg Trp Val Arg Arg Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu
1490 1495 1500

Met Ser Leu Phe Val Leu Ser Ser Lys Asp Gly Trp Val Asn Ile Met
1505 1510 1515 1520

Tyr Asp Gly Leu Asp Ala Val Gly Ile Asp Gln Gln Pro Val Gln Asn
1525 1530 1535

His Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val
1540 1545 1550

Ser Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe
1555 1560 1565

His Lys Cys Arg Gln His Gln Glu Ala Glu Glu Ala Arg Arg Arg Glu
1570 1575 1580

Glu Lys Arg Leu Arg Arg Leu Glu Arg Arg Arg Arg Lys Ala Gln Arg
1585 1590 1595 1600

Arg Pro Tyr Tyr Ala Asp Tyr Ser His Thr Arg Arg Ser Ile His Ser
1605 1610 1615

Leu Cys Thr Ser His Tyr Leu Asp Leu Phe Ile Thr Phe Ile Ile Cys
1620 1625 1630

Leu Asn Val Ile Thr Met Ser Met Glu His Tyr Asn Gln Pro Lys Ser
1635 1640 1645

Leu Asp Glu Ala Leu Lys Tyr Cys Asn Tyr Val Phe Thr Ile Val Phe
1650 1655 1660

Val Phe Glu Ala Ala Leu Lys Leu Val Ala Phe Gly Phe Arg Arg Phe
1665 1670 1675 1680

Phe Lys Asp Arg Trp Asn Gln Leu Asp Leu Ala Ile Val Leu Leu Ser
1685 1690 1695

Ile Met Gly Ile Ala Leu Glu Glu Ile Glu Met Asn Ala Ala Leu Pro
1700 1705 1710

Ile Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg
1715 1720 1725

Val Leu Lys Leu Leu Lys Met Ala Thr Gly Met Arg Ala Leu Leu Asp
1730 1735 1740

Thr Val Val Gln Ala Leu Pro Gln Val Gly Asn Leu Gly Leu Leu Phe
1745 1750 1755 1760

Met Leu Leu Phe Phe Ile Tyr Ala Ala Leu Gly Val Glu Leu Phe Gly
1765 1770 1775

Arg Leu Glu Cys Ser Glu Asp Asn Pro Cys Glu Gly Leu Ser Arg His
1780 1785 1790

Ala Thr Phe Thr Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg Val
1795 1800 1805

Ser Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp Thr Leu Arg Glu
1810 1815 1820

Cys Thr Arg Glu Asp Lys His Cys Leu Ser Tyr Leu Pro Ala Leu Ser
1825 1830 1835 1840

Pro Val Tyr Phe Val Thr Phe Met Leu Val Ala Gln Phe Val Leu Val
1845 1850 1855

Asn Val Val Val Ala Val Leu Met Lys His Leu Glu Glu Ser Asn Lys
1860 1865 1870

Glu Ala Arg Glu Asp Ala Glu Met Asp Ala Glu Ile Glu Leu Glu Met
1875 1880 1885

Ala Gln Gly Ser Thr Ala Gln Pro Pro Pro Thr Ala Gln Glu Ser Gln
1890 1895 1900

Gly Thr Gln Pro Asp Thr Pro Asn Leu Leu Val Val Arg Lys Val Ser
1905 1910 1915 1920

Val Ser Arg Met Leu Ser Leu Pro Asn Asp Ser Tyr Met Phe Arg Pro
1925 1930 1935

Val Ala Pro Ala Ala Ala Pro His Ser His Pro Leu Gln Glu Val Glu
1940 1945 1950

Met Glu Thr Tyr Thr Gly Pro Val Thr Ser Ala His Ser Pro Pro Leu
1955 1960 1965

Glu Pro Arg Ala Ser Phe Gln Val Pro Ser Ala Ala Ser Ser Pro Ala
1970 1975 1980

Arg Val Ser Asp Pro Leu Cys Ala Leu Ser Pro Arg Gly Thr Pro Arg
1985 1990 1995 2000

Ser Leu Ser Leu Ser Arg Ile Leu Cys Arg Gln Glu Ala Met His Ser
2005 2010 2015

Glu Ser Leu Glu Gly Lys Val Asp Asp Val Gly Gly Asp Ser Ile Pro
2020 2025 2030

Asp Tyr Thr Glu Pro Ala Glu Asn Met Ser Thr Ser Gln Ala Ser Thr
2035 2040 2045

Gly Ala Pro Arg Ser Pro Pro Cys Ser Pro Arg Pro Ala Ser Val Arg
2050 2055 2060

Thr Arg Lys His Thr Phe Gly Gln Arg Cys Ile Ser Ser Arg Pro Pro
2065 2070 2075 2080

Thr Leu Gly Gly Asp Glu Ala Glu Ala Ala Asp Pro Ala Asp Glu Glu
2085 2090 2095

Val Ser His Ile Thr Ser Ser Ala His Pro Trp Pro Ala Thr Glu Pro
2100 2105 2110

His Ser Pro Glu Ala Ser Pro Thr Ala Ser Pro Val Lys Gly Thr Met
2115 2120 2125

Gly Ser Gly Arg Asp Pro Arg Arg Phe Cys Ser Val Asp Ala Gln Ser
2130 2135 2140

Phe Leu Asp Lys Pro Gly Arg Pro Asp Ala Gln Arg Trp Ser Ser Val
2145 2150 2155 2160

Glu Leu Asp Asn Gly Glu Ser His Leu Glu Ser Gly Glu Val Arg Gly
2165 2170 2175

Arg Ala Ser Glu Leu Glu Pro Ala Leu Gly Ser Arg Arg Lys Lys Lys
2180 2185 2190

Met Ser Pro Pro Cys Ile Ser Ile Glu Pro Pro Thr Lys Asp Glu Gly
2195 2200 2205

Ser Ser Arg Pro Pro Ala Ala Glu Gly Gly Asn Thr Thr Leu Arg Arg
2210 2215 2220

Arg Thr Pro Ser Cys Glu Ala Ala Leu His Arg Asp Cys Pro Glu Pro
2225 2230 2235 2240

Thr Glu Gly Pro Gly Thr Gly Gly Asp Pro Val Ala Lys Gly Glu Arg
2245 2250 2255

Trp Gly Gln Ala Ser Cys Arg Ala Glu His Leu Thr Val Pro Asn Phe
2260 2265 2270

Ala Phe Glu Pro Leu Asp Met Gly Gly Pro Gly Gly Asp Cys Phe Leu
2275 2280 2285

Asp Ser Asp Gln Ser Val Thr Pro Glu Pro Arg Val Ser Ser Leu Gly
2290 2295 2300

Ala Ile Val Pro Leu Ile Leu Glu Thr Glu Leu Ser Met Pro Ser Pro
2305 2310 2315 2320

Asp Cys Pro Glu Lys Glu Gln Gly Leu Tyr Leu Thr Val Pro Gln Thr
2325 2330 2335

Pro Leu Lys Lys Pro Gly Ser Thr Pro Ala Thr Pro Ala Pro Asp Asp
2340 2345 2350

Ser Gly Asp Glu Pro Val Glx
2355

<210> 27
<211> 5735
<212> DNA
<213> rat

<400> 27
ccggcttcgg cgccgtgccc ggccacgtcc atgccaaggg ctccctgctc cacgctgaca 60
tggctgacag caacttaccg ccctcatctg cagcagcccc ggcccccgag ccgggaatca 120
ctgagcagcc ggggccccgg agtccccctc catcccctcc aggcctggag gagccattgg 180
aaggaaccaa ccctgacgtc ccacatccag acctggctcc tgttgctttc ttctgcctgc 240
gccagaccac gagcccacgg aactggtgca tcaagatggt ttgtaacccg tggttcgagt 300
gtgtgagcat gctggttatt ctgctgaact gtgtgaccct gggcatgtac cagccatgtg 360
atgacatgga gtgcctgtcg gaccgttgca agatcctgca ggtcttcgat gacttcatct 420
tcatcttctt tgccatggag atggtgctta agatggtggc cctgggcatt tttggcaaga 480
agtgctacct cggagacaca tggaaccgcc tggatttctt cattgtcatg gcagggatgg 540
ttgagtactc tctggaccta cagaacatca acctgtcagc catccgcact gtgcgtgtcc 600
tgaggcctct caaagccatc aaccgtgtac ccagcctgcg gatcctggtg aacctgctgc 660
tcgacacgct gcccatgctg gggaacgtgc tcctgctctg tttcttcgtc ttcttcatct 720
tcggcatcat tggcgtgcag ctctgggcag gcctgctacg gaaccgctgc ttcctggaag 780
aaaacttcac catacaaggg gatgtggccc tgccccctta ttaccaacca gaggaggatg 840
acgagatgcc ctttatctgc tccctgactg gggacaatgg catcatgggc tgccacgaga 900
tccccccact gaaggagcag ggccgggaag tctgcctgtc caaagatgat gtgtatgact 960
tcggggcggg gcgccaggac ctcaacgcca gcggtctgtg cgtcaactgg aaccgctact 1020
acaacgtctg ccgcacgggc aacgccaacc ctcacaaggg cgccatcaac tttgacaaca 1080
ttggctatgc ctggattgtg attttccagg tgatcactct ggaaggctgg gtggagatca 1140
tgtactatgt gatggacgca cattctttct acaacttcat tctgctcatc atagtgggct 1200
ccttcttcat gatcaacttg tgcctcgttc tcatagcaac ccagttctct gagaccaagc 1260
aacggaacca ccggctgatg ctggagcaac gccagcgcta cctgtcctcc agcacggtgg 1320
ccagttacgc tgagcccggt gattgctatg aggagatctt ccaatatgtc tgtcacatcc 1380
ttcgcaaagc caagcgccgt gccctaggcc tctaccaggc cctgcagaac cggcgccagg 1440
ccatgggccc ggggacacca gcccctgcca agcctgggcc ccatgccaag gagcccagcc 1500
actcgaagct gtgcccacga cacagccccc tggaccccac tccccacaca ctggtgcagc 1560
ccatctctgc cattctggcc tcttacccca gcagctgccc tcactgccag cacgaggcag 1620
gcaggcggcc ctctggcctg ggcagcactg actcaggcca ggaaggctca ggttctggtg 1680
gctctgcaga ggccgaagcc aatggggatg gactccagag cagagaggat ggggtctcct 1740
cggacctggg gaaggaggag gaacaggagg acggggcagc ccgactgtgt ggggatgtat 1800
ggcgcgagac acgaaaaaag ctgcggggca tcgtggacag caagtacttc aacagaggta 1860
tcatgatggc tatcctggtg aacacagtca gcatgggcat cgagcaccac gaacagcccg 1920

aggagctgac caacatcctg gagatctgca atgtggtctt caccagtatg tttgccctgg 1980
agatgatcct gaaactggcc gcctttgggc tcttcgacta cctgcggaac ccttacaaca 2040
tctttgacag catcatcgtc atcatcagca tctgggaaat cgtggggcag gcggacagtg 2100
gcctgtctgt gctgcgcact tcccggttgc tgcgggtgct gaagctagtg cgcttcatgc 2160
cggcgctgcg ccagctcgtg gtgctcatga agaccatgga caacgtggcc accttctgca 2220
tgctactcat gctgttcatc ttcatcttca gcatccttgg gatcgatatc tttggctgca 2280
aattcagcct ccgcacggac acgggagaca ccgttcctga caggaagaac ttcgattcct 2340
tactgtgggc catcgtcaca gtgttccaga tcctcactca ggaggactgg aacgttgtcc 2400
tgtacaatgg catggcctcc accacccccc gggcctccct ctattttgtt gccctcatga 2460
cctttggcaa ctacgttctc ttcaatctcc tggtggctat cctggtagag ggtttccagg 2520
ctgagggtga tgctaatcgt tcctactctg atgaggacca gagctcatcc aatttagagg 2580
agttagacaa gctcccagag ggcctggaca acaggagaga tctcaagctc tgcccaatac 2640
ccatgacacc caatggacac ctggacccta gcctccctct gggtgcgcat ctgggtcctg 2700
ctggtaccat gggtactgcc ccccgcctct cactgcagcc agacccggta ctggtggccc 2760
gggactctcg gaaaagcagt tactggtccc tgggcaggat gagctatgat cagcgatcct 2820
tgtccagctc ccggagctcc tactacggcc ctgggggccg cagtgggacc tgggctagcc 2880
gccgctccag ctggaacagc ctgaaacaca agccgccctc agctgagcat gagtccttac 2940
tgtctgggga gggtggaggt agctgcgtca gggcctgtga aggcgcccgg gaggaggcgc 3000
caactcgcac cgcacccctg catgctccac accggcacca cgcgcaccat ggaccccacc 3060
tggcacaccg tcaccgacac caccgccgga ctctgtccct cgataccagg gactctgttg 3120
acctgggaga gctggtgccc gtggtgggtg cccactcacg ggccgcttgg agggggggcgg 3180
gtcaggcccc tgggcacgag gactgcaatg gcagaatgcc caacatggcc aaggatgtct 3240
tcaccaagat ggatgaccgc cgcgaccgcg gggaggacga ggaggagatc gactataccc 3300
tgtgtttccg ggtccgcaag atgatttgct gtgtgtacaa gccggactgg tgcgaagtcc 3360
gcgaggactg gtcggtctac ctcttctccc ccgagaacaa gttccggatc ctgtgtcaga 3420
ctatcattgc tcacaagctt tttgactacg tggtcttggc ctttatcttc ctcaactgta 3480
tcaccattgc tctggagaga ccccagattg aagctggtag cactgagcgc atcttcctca 3540
cggtgtctaa ctacatcttc acagccatct tcgtgggcga gatgacactg aaggtggttt 3600
ctctgggcct gtactttggt gagcaggcgt acctgcgtac ggactggaat gtactggatg 3660
gtttcctggt ctttgtgtcc atcatcgata tcgtagtgtc cgtggcctct gctgggggag 3720
ccaagattct gggggtcctg cggctcctgc gtaccttacg tcctttgaga gttatcagcc 3780
gggcccctgg gctgaagctg gtggtagaga cgctcatctc ctccctcaag cccattggga 3840
acatcgtcct catctgctgt gccttcttca tcatcttcgg catcctgggg gtgcagcttt 3900
tcaaaggcaa gttctaccat tgtttgggag tggacacccg aaacatcacc aaccgatctg 3960
actgcgtggc ggccaactac cgctgggtgc atcacaaata caactttgac aacctgggcc 4020
aggcattgat gtccctcttt gtcttggcct ccaaggacgg ctgggtgaac atcatgtata 4080
atggattaga tgctgttgct gtggaccagc agcccgtgac gaaccacaac ccctggatgc 4140
tactgtactt catttcgttc ctgctcatcg tcagcttctt tgtgctcaac atgtttgtgg 4200
gcgtggtcgt ggagaacttc cacaagtgcc ggcagcacca ggaggctgag gaggcgcgga 4260
ggcgtgagga gaaacggctg cggcgcctgg aaaagaagcg ccgttacgct cagaggctgc 4320
cctactatgc tacctactgt cccacaaggc tgctcatcca ctccatgtgc accagccact 4380
acctggacat cttcattacc ttcatcatct gcctcaatgt tgtcaccatg tccctggagc 4440
actacaacca gcctacatcc ctagagacag cccttaagta ctgcaactac atgttcacca 4500
ctgtgtttgt gctggaggct gtgctgaagc tggtggcatt tggcctgagg cgtttcttca 4560
aggaccgatg gaaccagctg gacctggcca ttgtgctgct gtccgtcatg ggcatcacac 4620
tggaggagat cgagatcaat gccgcccttc ccatcaaccc caccatcatc cgtatcatgc 4680
gtgttctgcg tatcgcccgg gtgttgaagc tattgaagat ggccacagga atgcgggccc 4740
tgctggacac agtggtacag gctctgcccc aggtgggcaa cctgggcctg ctcttcatgc 4800

tgctcttctt catctatgct gctctgggag tggagctctt cggaaagctg gtctgcaatg 4860
acgagaaccc gtgtgagggt atgagccggc acgccacctt tgaaaactct gctagggcct 4920
tcctcacgct cttccaggtc tccacaggcg ataactggaa tggaattatg aaggacaccc 4980
tgcgagactg tacccatgat gagcgcacgt gcctaagcag cctgcagttt gtgtcaccgc 5040
tctactttgt gagcttcgtg ctcacagctc agttcgtgct catcaacgtg gtggtggccg 5100
tgctgatgaa acatctggat gacagcaaca aggaggccca ggaggatgca gagatggatg 5160
ctgagatcga gctggagatg gcccatggct ccggcccctg ccctggcccc tgccctggtc 5220
cctgcccctg cccctgcccc tgcccctgtt ctggcccgag gtgcccacta gttacctggg 5280
gctcgggggc gatggatcgg gaggggcagg tgctggaggc acaccgagag tcacctgtgc 5340
gcactgctat caggtgctgg acaccgagag tcacctgtgc cggcactgct attctccagc 5400
ccaggagacc ctgtggctgg acagggtctc tttaatcatc aaggactcct tggaggggga 5460
gctgaccatc attgacaacc tgtctgggtc cgtcttccac cactacgcct cactgacggc 5520
tgtggcaagt gtcaccatga caagcaagag gtgcagctgg ctgagacaga ggccttctcc 5580
ctgaactcag acaggtcttc atccatcctg ctgggggatg acctgagtct tgaggacccc 5640
acggcctcgc acagggcccc aaaggagagc aagggtgaac aataaagagc ctccggagcc 5700
catgcaggct ggagacctgg atgaatgcaa aaaaa 5735

<210> 28
<211> 1792
<212> PRT
<213> rat

<400> 28
Met Ala Asp Ser Asn Leu Pro Pro Ser Ser Ala Ala Ala Pro Ala Pro
1 5 10 15

Glu Pro Gly Ile Thr Glu Gln Pro Gly Pro Arg Ser Pro Pro Pro Ser
20 25 30

Pro Pro Gly Leu Glu Glu Pro Leu Glu Gly Thr Asn Pro Asp Val Pro
35 40 45

His Pro Asp Leu Ala Pro Val Ala Phe Phe Cys Leu Arg Gln Thr Thr
50 55 60

Ser Pro Arg Asn Trp Cys Ile Lys Met Val Cys Asn Pro Trp Phe Glu
65 70 75 80

Cys Val Ser Met Leu Val Ile Leu Leu Asn Cys Val Thr Leu Gly Met
85 90 95

Tyr Gln Pro Cys Asp Asp Met Glu Cys Leu Ser Asp Arg Cys Lys Ile
100 105 110

Leu Gln Val Phe Asp Asp Phe Ile Phe Ile Phe Phe Ala Met Glu Met
115 120 125

Val Leu Lys Met Val Ala Leu Gly Ile Phe Gly Lys Lys Cys Tyr Leu

130 135 140

Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val Met Ala Gly Met
145 150 155 160

Val Glu Tyr Ser Leu Asp Leu Gln Asn Ile Asn Leu Ser Ala Ile Arg
165 170 175

Thr Val Arg Val Leu Arg Pro Leu Lys Ala Ile Asn Arg Val Pro Ser
180 185 190

Leu Arg Ile Leu Val Asn Leu Leu Leu Asp Thr Leu Pro Met Leu Gly
195 200 205

Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile Phe Gly Ile Ile
210 215 220

Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu Glu
225 230 235 240

Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
245 250 255

Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Thr Gly Asp
260 265 270

Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
275 280 285

Arg Glu Val Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
290 295 300

Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
305 310 315 320

Tyr Asn Val Cys Arg Thr Gly Asn Ala Asn Pro His Lys Gly Ala Ile
325 330 335

Asn Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln Val Ile
340 345 350

Thr Leu Glu Gly Trp Val Glu Ile Met Tyr Tyr Val Met Asp Ala His
355 360 365

Ser Phe Tyr Asn Phe Ile Leu Leu Ile Ile Val Gly Ser Phe Phe Met
370 375 380

Ile Asn Leu Cys Leu Val Leu Ile Ala Thr Gln Phe Ser Glu Thr Lys

385 390 395 400

Gln Arg Asn His Arg Leu Met Leu Glu Gln Arg Gln Arg Tyr Leu Ser
405 410 415

Ser Ser Thr Val Ala Ser Tyr Ala Glu Pro Gly Asp Cys Tyr Glu Glu
420 425 430

Ile Phe Gln Tyr Val Cys His Ile Leu Arg Lys Ala Lys Arg Arg Ala
435 440 445

Leu Gly Leu Tyr Gln Ala Leu Gln Asn Arg Arg Gln Ala Met Gly Pro
450 455 460

Gly Thr Pro Ala Pro Ala Lys Pro Gly Pro His Ala Lys Glu Pro Ser
465 470 475 480

His Ser Lys Leu Cys Pro Arg His Ser Pro Leu Asp Pro Thr Pro His
485 490 495

Thr Leu Val Gln Pro Ile Ser Ala Ile Leu Ala Ser Tyr Pro Ser Ser
500 505 510

Cys Pro His Cys Gln His Glu Ala Gly Arg Arg Pro Ser Gly Leu Gly
515 520 525

Ser Thr Asp Ser Gly Gln Glu Gly Ser Gly Ser Gly Gly Ser Ala Glu
530 535 540

Ala Glu Ala Asn Gly Asp Gly Leu Gln Ser Arg Glu Asp Gly Val Ser
545 550 555 560

Ser Asp Leu Gly Lys Glu Glu Glu Gln Glu Asp Gly Ala Ala Arg Leu
565 570 575

Cys Gly Asp Val Trp Arg Glu Thr Arg Lys Lys Leu Arg Gly Ile Val
580 585 590

Asp Ser Lys Tyr Phe Asn Arg Gly Ile Met Met Ala Ile Leu Val Asn
595 600 605

Thr Val Ser Met Gly Ile Glu His His Glu Gln Pro Glu Glu Leu Thr
610 615 620

Asn Ile Leu Glu Ile Cys Asn Val Val Phe Thr Ser Met Phe Ala Leu
625 630 635 640

Glu Met Ile Leu Lys Leu Ala Ala Phe Gly Leu Phe Asp Tyr Leu Arg

645 650 655

Asn Pro Tyr Asn Ile Phe Asp Ser Ile Ile Val Ile Ile Ser Ile Trp
660 665 670

Glu Ile Val Gly Gln Ala Asp Ser Gly Leu Ser Val Leu Arg Thr Ser
675 680 685

Arg Leu Leu Arg Val Leu Lys Leu Val Arg Phe Met Pro Ala Leu Arg
690 695 700

Gln Leu Val Val Leu Met Lys Thr Met Asp Asn Val Ala Thr Phe Cys
705 710 715 720

Met Leu Leu Met Leu Phe Ile Phe Ile Phe Ser Ile Leu Gly Ile Asp
725 730 735

Ile Phe Gly Cys Lys Phe Ser Leu Arg Thr Asp Thr Gly Asp Thr Val
740 745 750

Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp Ala Ile Val Thr Val
755 760 765

Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Val Val Leu Tyr Asn Gly
770 775 780

Met Ala Ser Thr Thr Pro Trp Ala Ser Leu Tyr Phe Val Ala Leu Met
785 790 795 800

Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu Val Ala Ile Leu Val
805 810 815

Glu Gly Phe Gln Ala Glu Gly Asp Ala Asn Arg Ser Tyr Ser Asp Glu
820 825 830

Asp Gln Ser Ser Ser Asn Leu Glu Glu Leu Asp Lys Leu Pro Glu Gly
835 840 845

Leu Asp Asn Arg Arg Asp Leu Lys Leu Cys Pro Ile Pro Met Thr Pro
850 855 860

Asn Gly His Leu Asp Pro Ser Leu Pro Leu Gly Ala His Leu Gly Pro
865 870 875 880

Ala Gly Thr Met Gly Thr Ala Pro Arg Leu Ser Leu Gln Pro Asp Pro
885 890 895

Val Leu Val Ala Arg Asp Ser Arg Lys Ser Ser Tyr Trp Ser Leu Gly

900 905 910

Arg Met Ser Tyr Asp Gln Arg Ser Leu Ser Ser Ser Arg Ser Ser Tyr
915 920 925

Tyr Gly Pro Gly Gly Arg Ser Gly Thr Trp Ala Ser Arg Arg Ser Ser
930 935 940

Trp Asn Ser Leu Lys His Lys Pro Pro Ser Ala Glu His Glu Ser Leu
945 950 955 960

Leu Ser Gly Glu Gly Gly Gly Ser Cys Val Arg Ala Cys Glu Gly Ala
965 970 975

Arg Glu Glu Ala Pro Thr Arg Thr Ala Pro Leu His Ala Pro His Arg
980 985 990

His His Ala His His Gly Pro His Leu Ala His Arg His Arg His His
995 1000 1005

Arg Arg Thr Leu Ser Leu Asp Thr Arg Asp Ser Val Asp Leu Gly Glu
1010 1015 1020

Leu Val Pro Val Val Gly Ala His Ser Arg Ala Ala Trp Arg Gly Ala
1025 1030 1035 1040

Gly Gln Ala Pro Gly His Glu Asp Cys Asn Gly Arg Met Pro Asn Met
1045 1050 1055

Ala Lys Asp Val Phe Thr Lys Met Asp Asp Arg Arg Asp Arg Gly Glu
1060 1065 1070

Asp Glu Glu Glu Ile Asp Tyr Thr Leu Cys Phe Arg Val Arg Lys Met
1075 1080 1085

Ile Cys Cys Val Tyr Lys Pro Asp Trp Cys Glu Val Arg Glu Asp Trp
1090 1095 1100

Ser Val Tyr Leu Phe Ser Pro Glu Asn Lys Phe Arg Ile Leu Cys Gln
1105 1110 1115 1120

Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val Leu Ala Phe Ile
1125 1130 1135

Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro Gln Ile Glu Ala
1140 1145 1150

Gly Ser Thr Glu Arg Ile Phe Leu Thr Val Ser Asn Tyr Ile Phe Thr

1155 1160 1165

Ala Ile Phe Val Gly Glu Met Thr Leu Lys Val Val Ser Leu Gly Leu
1170 1175 1180

Tyr Phe Gly Glu Gln Ala Tyr Leu Arg Thr Asp Trp Asn Val Leu Asp
1185 1190 1195 1200

Gly Phe Leu Val Phe Val Ser Ile Ile Asp Ile Val Val Ser Val Ala
1205 1210 1215

Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg Leu Leu Arg Thr
1220 1225 1230

Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Pro Gly Leu Lys Leu Val
1235 1240 1245

Val Glu Thr Leu Ile Ser Ser Leu Lys Pro Ile Gly Asn Ile Val Leu
1250 1255 1260

Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu Gly Val Gln Leu
1265 1270 1275 1280

Phe Lys Gly Lys Phe Tyr His Cys Leu Gly Val Asp Thr Arg Asn Ile
1285 1290 1295

Thr Asn Arg Ser Asp Cys Val Ala Ala Asn Tyr Arg Trp Val His His
1300 1305 1310

Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met Ser Leu Phe Val
1315 1320 1325

Leu Ala Ser Lys Asp Gly Trp Val Asn Ile Met Tyr Asn Gly Leu Asp
1330 1335 1340

Ala Val Ala Val Asp Gln Gln Pro Val Thr Asn His Asn Pro Trp Met
1345 1350 1355 1360

Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ser Phe Phe Val Leu
1365 1370 1375

Asn Met Phe Val Gly Val Val Val Glu Asn Phe His Lys Cys Arg Gln
1380 1385 1390

His Gln Glu Ala Glu Glu Ala Arg Arg Arg Glu Glu Lys Arg Leu Arg
1395 1400 1405

Arg Leu Glu Lys Lys Arg Arg Tyr Ala Gln Arg Leu Pro Tyr Tyr Ala

1410 1415 1420

Thr Tyr Cys Pro Thr Arg Leu Leu Ile His Ser Met Cys Thr Ser His
1425 1430 1435 1440

Tyr Leu Asp Ile Phe Ile Thr Phe Ile Ile Cys Leu Asn Val Val Thr
1445 1450 1455

Met Ser Leu Glu His Tyr Asn Gln Pro Thr Ser Leu Glu Thr Ala Leu
1460 1465 1470

Lys Tyr Cys Asn Tyr Met Phe Thr Thr Val Phe Val Leu Glu Ala Val
1475 1480 1485

Leu Lys Leu Val Ala Phe Gly Leu Arg Arg Phe Phe Lys Asp Arg Trp
1490 1495 1500

Asn Gln Leu Asp Leu Ala Ile Val Leu Leu Ser Val Met Gly Ile Thr
1505 1510 1515 1520

Leu Glu Glu Ile Glu Ile Asn Ala Ala Leu Pro Ile Asn Pro Thr Ile
1525 1530 1535

Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg Val Leu Lys Leu Leu
1540 1545 1550

Lys Met Ala Thr Gly Met Arg Ala Leu Leu Asp Thr Val Val Gln Ala
1555 1560 1565

Leu Pro Gln Val Gly Asn Leu Gly Leu Leu Phe Met Leu Leu Phe Phe
1570 1575 1580

Ile Tyr Ala Ala Leu Gly Val Glu Leu Phe Gly Lys Leu Val Cys Asn
1585 1590 1595 1600

Asp Glu Asn Pro Cys Glu Gly Met Ser Arg His Ala Thr Phe Glu Asn
1605 1610 1615

Ser Ala Arg Ala Phe Leu Thr Leu Phe Gln Val Ser Thr Gly Asp Asn
1620 1625 1630

Trp Asn Gly Ile Met Lys Asp Thr Leu Arg Asp Cys Thr His Asp Glu
1635 1640 1645

Arg Thr Cys Leu Ser Ser Leu Gln Phe Val Ser Pro Leu Tyr Phe Val
1650 1655 1660

Ser Phe Val Leu Thr Ala Gln Phe Val Leu Ile Asn Val Val Val Ala

1665 1670 1675 1680

Val Leu Met Lys His Leu Asp Asp Ser Asn Lys Glu Ala Gln Glu Asp
1685 1690 1695

Ala Glu Met Asp Ala Glu Ile Glu Leu Glu Met Ala His Gly Ser Gly
1700 1705 1710

Pro Cys Pro Gly Pro Cys Pro Gly Pro Cys Pro Cys Pro Cys Pro Cys
1715 1720 1725

Pro Cys Ser Gly Pro Arg Cys Pro Leu Val Thr Trp Gly Ser Gly Ala
1730 1735 1740

Met Asp Arg Glu Gly Gln Val Leu Glu Ala His Arg Glu Ser Pro Val
1745 1750 1755 1760

Arg Thr Ala Ile Arg Cys Trp Thr Pro Arg Val Thr Cys Ala Gly Thr
1765 1770 1775

Ala Ile Leu Gln Pro Arg Arg Pro Cys Gly Trp Thr Gly Ser Leu Glx
1780 1785 1790

<210> 29
<211> 540
<212> DNA
<213> rat

<400> 29
aagcttctct gagccaggca gctgctatga ggagctactc aagtacctgg tgtacatcct 60
ccgaaaagca gcccgaaggc tggcccaggt ctctagggct ataggcgtgc gggctgggct 120
gctcagcagc ccagtggccc gtagtgggca ggagccccag cccagtggca gctgcactcg 180
ctcacaccgt cgtctgtctg tccaccacct ggtccaccac catcaccacc accatcacca 240
ctaccacctg ggtaatggga cgctcagagt tccccgggcc agcccagaga tccaggacag 300
ggatgccaat gggtctcgcc ggctcatgct accaccaccc tctacaccca ctccctctgg 360
gggccctccg aggggtgcgg agtctgtaca cagcttctac catgctgact gccacttgga 420
gccagtccgt tgccaggcac cccctcccag atgcccatcg gaggcatctg gtaggactgt 480
gggtagtggg aaggtgtacc ccactgtgca taccagccct ccaccagaga tactgaagga 540

<210> 30
<211> 2212
<212> DNA
<213> HUMAN

<400> 30
gtgaggggga gccggccggc tggcccggga agccccaggg gcgcagggga agcgggactc 60
gcgccgggcg gggtttccct gcgccccggc gccccgcggg cagcatgccc ctgcgggcag 120
ggggagctgg gctgaactgg ccctcccggg ggctcagctt gcgccctaga gcccaccaga 180
tgtgcccccg ccggggcccc cgggttgcgt gaggacacct cctctgaggg gcgccgcttg 240
cccctctccg gatcgcccgg ggccccggct ggccagagga tggacgagga ggaggatgga 300
gcgggcgccg aggagtcggg acagccccgg agcttcatgc ggctcaacga cctgtcgggg 360
gccgggggcc ggccggggcc ggggtcagca gaaaaggacc cgggcagcgc ggactccgag 420
gcggaggggc tgccgtaccc ggcgctggcc ccggtggttt tcttctactt gagccaggac 480
agccgcccgc ggagctggtg tctccgcacg gtctgtaacc cctggtttga gcgcatcagc 540
atgttggtca tccttctcaa ctgcgtgacc ctgggcatgt tccggccatg cgaggacatc 600
gcctgtgact cccagcgctg ccggatcctg caggcctttg atgacttcat ctttgccttc 660
tttgccgtgg agatggtggt gaagatggtg gccttgggca tctttgggaa aaagtgttac 720
ctgggagaca cttggaaccg gcttgacttt ttcatcgtca tcgcagggat gctggagtac 780
tcgctggacc tgcagaacgt cagcttctca gctgtcagga cagtccgtgt gctgcgaccg 840
ctcagggcca ttaaccgggt gcccagcatg cgcatccttg tcacgttgct gctggatacg 900
ctgcccatgc tgggcaacgt cctgctgctc tgcttcttcg tcttcttcat cttcggcatc 960
gtcggcgtcc agctgtgggc agggctgctt cggaaccgat gcttcctacc tgagaatttc 1020
agcctccccc tgagcgtgga cctggagcgc tattaccaga cagagaacga ggatgagagc 1080
cccttcatct gctcccagcc acgcgagaac ggcatgcggt cctgcagaag cgtgcccacg 1140
ctgcgcgggg acgggggcgg tggcccacct tgcggtctgg actatgaggc ctacaacagc 1200
tccagcaaca ccacctgtgt caactggaac cagtactaca ccaactgctc agcgggggag 1260
cacaaccccct tcaagggcgc catcaacttt gacaacattg gctatgcctg gatcgccatc 1320
ttccaggtca tcacgctgga gggctgggtc gacatcatgt actttgtgat ggatgctcat 1380
tccttctaca atttcatcta cttcatcctc ctcatcatcg tgggctcctt cttcatgatc 1440
aacctgtgcc tggtggtgat tgccacgcag ttctcagaga ccaagcagcg ggaaagccag 1500
ctgatgcggg agcagcgtgt gcggttcctg tccaacgcca gcaccctggc tagcttctct 1560
gagcccggca gctgctatga ggagctgctc aagtacctgg tgtacatcct tcgtaaggca 1620
gcccgcaggc tggctcaggt ctctcgggca gcaggtgtgc gggttgggct gctcagcagc 1680
ccagcacccc tcgggggcca ggagacccag cccagcagca gctgctctcg ctcccaccgc 1740
cgcctatccg tccaccacct ggtgcaccac caccaccacc atcaccacca ctaccacctg 1800
ggcaatggga cgctcagggc cccccgggcc agcccggaga tccaggacag ggatgccaat 1860
gggtcccgcc ggctcatgct gccaccaccc tcgacgcctg ccctctccgg ggccccccct 1920
ggtggcgcag agtctgtgca cagcttctac catgccgact gccacttaga gccagtccgc 1980
tgccaggcgc cccctcccag gtccccatct gaggcatccg gcaggactgt gggcagcggg 2040
aaggtgtatc ccaccgtgca caccagccct ccaccggaga cgctgaagga gaaggcacta 2100
gtagaggtgg ctgccagctc tgggccccca accctcacca gcctcaacat cccacccggg 2160
ccctacagct ccatgcacaa gctgctggag acacagagta caggtgcctg cc 2212

<210> 31
<211> 644
<212> PRT
<213> HUMAN

<400> 31
Met Asp Glu Glu Glu Asp Gly Ala Gly Ala Glu Glu Ser Gly Gln Pro
1 5 10 15

```
Arg Ser Phe Met Arg Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Pro
            20                  25                  30

Gly Pro Gly Ser Ala Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala
        35                  40                  45

Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu
    50                  55                  60

Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
65                  70                  75                  80

Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val
                85                  90                  95

Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln
            100                 105                 110

Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe
        115                 120                 125

Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys
    130                 135                 140

Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val
145                 150                 155                 160

Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe
                165                 170                 175

Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn
            180                 185                 190

Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu
        195                 200                 205

Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile
    210                 215                 220

Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg
225                 230                 235                 240

Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu
                245                 250                 255

Arg Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser
            260                 265                 270
```

Gln Pro Arg Glu Asn Gly Met Arg Ser Cys Arg Ser Val Pro Thr Leu
275 280 285

Arg Gly Asp Gly Gly Gly Gly Pro Pro Cys Gly Leu Asp Tyr Glu Ala
290 295 300

Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr
305 310 315 320

Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn
325 330 335

Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr
340 345 350

Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser
355 360 365

Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe
370 375 380

Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu
385 390 395 400

Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe
405 410 415

Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys
420 425 430

Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala
435 440 445

Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu
450 455 460

Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser
465 470 475 480

Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His
485 490 495

His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu
500 505 510

Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly
515 520 525

Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Ala Leu Ser Gly
530 535 540

Ala Pro Pro Gly Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp
545 550 555 560

Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Ser Pro
565 570 575

Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr
580 585 590

Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val
595 600 605

Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile
610 615 620

Pro Pro Gly Pro Tyr Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser
625 630 635 640

Thr Gly Ala Cys

<210> 32
<211> 1608
<212> DNA
<213> HUMAN

<400> 32
atgcccgcgg ggacgccgcc ggccagcaga gcgaggtgct gccggccgcc accatgaccg 60
agggcgcacg ggccgccgac gaggtccggg tgcccctggg cgcgccgccc cctggccctg 120
cggcgttggt gggggcgtcc ccggagagcc ccggggcgcc gggacgcgag gcggagcggg 180
ggtccgagct cggcgtgtca ccctccgaga gcccggcggc cgagcgcggc gcggagctgg 240
gtgccgacga ggagcagcgc gtcccgtacc cggccttggc ggccacggtc ttcttctgcc 300
tcggtcagac cacgcggccg cgcagctggt gcctccggct ggtctgcaac ccatggttcg 360
agcacgtgag catgctggta atcatgctca actgcgtgac cctgggcatg ttccggccct 420
gtgaggacgt tgagtgcggc tccgagcgct gcaacatcct ggaggccttt gacgccttca 480
ttttcgcctt ttttgcggtg gagatggtca tcaagatggt ggccttgggg ctgttcgggc 540
agaagtgtta cctgggtgac acgtggaaca ggctggattt cttcatcgtc gtggcgggca 600
tgatggagta ctcgttggac ggacacaacg tgagcctctc ggctatcagg accgtgcggg 660
tgctgcggcc cctccgcgcc atcaaccgcg tgcctagcat gcggatcctg gtcactctgc 720
tgctggatac gctgcccatg ctcgggaacg tccttctgct gtgcttcttc gtcttcttca 780
ttttcggcat cgttggcgtc cagctctggg ctggcctcct gcggaaccgc tgcttcctgg 840
acagtgcctt tgtcaggaac aacaacctga ccttcctgcg gccgtactac cagacggagg 900
agggcgagga gaacccgttc atctgctcct cacgccgaga caacggcatg cagaagtgct 960
cgcacatccc cggccgccgc gagctgcgca tgccctgcac cctgggctgg gaggcctaca 1020

cgcagccgca ggccgagggg gtgggcgctg cacgcaacgc ctgcatcaac tggaaccagt 1080
actacaacgt gtgccgctcg ggtgactcca acccccacaa cggtgccatc aacttcgaca 1140
acatcggcta cgcctggatc gccatcttcc aggtgatcac gctggaaggc tgggtggaca 1200
tcatgtacta cgtcatggac gcccactcat tctacaactt catctatttc atcctgctca 1260
tcatcgtggg ctccttcttc atgatcaacc tgtgcctggt ggtgattgcc acgcagttct 1320
cggagacgaa gcagcgggag agtcagctga tgcgggagca gcgggcacgc cacctgtcca 1380
acgacagcac gctggccagc ttctccgagc ctggcagctg ctacgaagag ctgctgaagt 1440
acgtgggcca catattccgc aaggtcaagc ggcgcagctt gcgcctctac gcccgctggc 1500
agagccgctg gcgcaagaag gtggacccca gtgctgtgca aggccagggt cccgggcacc 1560
gccagcgccg ggcaggcagg cacacagcct cggtgcacca cctggtct 1608

<210> 33
<211> 518
<212> PRT
<213> HUMAN

<400> 33
Met Thr Glu Gly Ala Arg Ala Ala Asp Glu Val Arg Val Pro Leu Gly
1 5 10 15

Ala Pro Pro Pro Gly Pro Ala Ala Leu Val Gly Ala Ser Pro Glu Ser
20 25 30

Pro Gly Ala Pro Gly Arg Glu Ala Glu Arg Gly Ser Glu Leu Gly Val
35 40 45

Ser Pro Ser Glu Ser Pro Ala Ala Glu Arg Gly Ala Glu Leu Gly Ala
50 55 60

Asp Glu Glu Gln Arg Val Pro Tyr Pro Ala Leu Ala Ala Thr Val Phe
65 70 75 80

Phe Cys Leu Gly Gln Thr Thr Arg Pro Arg Ser Trp Cys Leu Arg Leu
85 90 95

Val Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu
100 105 110

Asn Cys Val Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Val Glu Cys
115 120 125

Gly Ser Glu Arg Cys Asn Ile Leu Glu Ala Phe Asp Ala Phe Ile Phe
130 135 140

Ala Phe Phe Ala Val Glu Met Val Ile Lys Met Val Ala Leu Gly Leu
145 150 155 160

Phe Gly Gln Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe

```
                165                 170                 175

Phe Ile Val Val Ala Gly Met Met Glu Tyr Ser Leu Asp Gly His Asn
            180                 185                 190

Val Ser Leu Ser Ala Ile Arg Thr Val Arg Val Leu Arg Pro Leu Arg
        195                 200                 205

Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu
    210                 215                 220

Asp Thr Leu Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val
225                 230                 235                 240

Phe Phe Ile Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu
                245                 250                 255

Arg Asn Arg Cys Phe Leu Asp Ser Ala Phe Val Arg Asn Asn Asn Leu
            260                 265                 270

Thr Phe Leu Arg Pro Tyr Tyr Gln Thr Glu Glu Gly Glu Glu Asn Pro
        275                 280                 285

Phe Ile Cys Ser Ser Arg Arg Asp Asn Gly Met Gln Lys Cys Ser His
    290                 295                 300

Ile Pro Gly Arg Arg Glu Leu Arg Met Pro Cys Thr Leu Gly Trp Glu
305                 310                 315                 320

Ala Tyr Thr Gln Pro Gln Ala Glu Gly Val Gly Ala Ala Arg Asn Ala
                325                 330                 335

Cys Ile Asn Trp Asn Gln Tyr Tyr Asn Val Cys Arg Ser Gly Asp Ser
            340                 345                 350

Asn Pro His Asn Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala Trp
        355                 360                 365

Ile Ala Ile Phe Gln Val Ile Thr Leu Glu Gly Trp Val Asp Ile Met
    370                 375                 380

Tyr Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile
385                 390                 395                 400

Leu Leu Ile Ile Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val
                405                 410                 415

Val Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu Ser Gln Leu
```

420 425 430

Met Arg Glu Gln Arg Ala Arg His Leu Ser Asn Asp Ser Thr Leu Ala
435 440 445

Ser Phe Ser Glu Pro Gly Ser Cys Tyr Glu Glu Leu Leu Lys Tyr Val
450 455 460

Gly His Ile Phe Arg Lys Val Lys Arg Arg Ser Leu Arg Leu Tyr Ala
465 470 475 480

Arg Trp Gln Ser Arg Trp Arg Lys Lys Val Asp Pro Ser Ala Val Gln
485 490 495

Gly Gln Gly Pro Gly His Arg Gln Arg Arg Ala Gly Arg His Thr Ala
500 505 510

Ser Val His His Leu Val
515

<210> 34
<211> 1080
<212> DNA
<213> HUMAN

<400> 34
gcagtgtcat gtctctaggg aggatgagct atgaccagcg ctccctgtcc agctcccgga 60
gctcctacta cgggccatgg ggccgcagcg cggcctgggc cagccgtcgc tccagctgga 120
acagcctcaa gcacaagccg ccgtcggcgg agcatgagtc cctgctctct gcggagcgcg 180
gcggcggcgc ccgggtctgc gaggttgccg cggacgaggg gccgccgcgg gccgcacccc 240
tgcacacccc acacgcccac cacattcatc acgggcccca tctggcgcac cgccaccgcc 300
accaccgccg gacgctgtcc ctcgacaaca gggactcggt ggacctggcc gagctggtgc 360
ccgcggtggg cgcccacccc cgggccgcct ggagggcggc aggcccggcc cccgggcatg 420
aggactgcaa tggcaggatg cccagcatcg ccaaagacgt cttcaccaag atgggcgacc 480
gcggggatcg cggggaggat gaggaggaaa tcgactacac cctgtgcttc cgcgtccgca 540
agatgatcga cgtctataag cccgactggt gcgaggtccg cgaagactgg tctgtctacc 600
tcttctctcc cgagaacagg ttccgggtcc tgtgtcagac cattattgcc cacaaactct 660
tcgactacgt cgtcctggcc ttcatctttc tcaactgcat caccatcgcc ctggagcggc 720
ctcagatcga ggccggcagc accgaacgca tctttctcac cgtgtccaac tacatcttca 780
cggccatctt cgtgggcgag atgacattga aggtagtctc gctgggcctg tacttcggcg 840
agcaggcgta cctacgcagc agctggaacg tgctggatgg ctttcttgtc ttcgtgtcca 900
tcatcgacat cgtggtgtcc ctggcctcag ccgggggagc caagatcttg gggtcctcc 960
gagtcttgcg gctcctgcgc accctacgcc ccctgcgtgt catcagccgg gcgccgggcc 1020
tgaagctggt ggtggagaca ctcatctcct ccctcaagcc catcggcaac atcgtgctca 1080

<210> 35
<211> 359

<212> PRT
<213> HUMAN

<400> 35

```
Ser Val Met Ser Leu Gly Arg Met Ser Tyr Asp Gln Arg Ser Leu Ser
 1               5                  10                  15

Ser Ser Arg Ser Ser Tyr Tyr Gly Pro Trp Gly Arg Ser Ala Ala Trp
            20                  25                  30

Ala Ser Arg Arg Ser Ser Trp Asn Ser Leu Lys His Lys Pro Pro Ser
        35                  40                  45

Ala Glu His Glu Ser Leu Leu Ser Ala Glu Arg Gly Gly Gly Ala Arg
    50                  55                  60

Val Cys Glu Val Ala Ala Asp Glu Gly Pro Pro Arg Ala Ala Pro Leu
65                  70                  75                  80

His Thr Pro His Ala His His Ile His His Gly Pro His Leu Ala His
                85                  90                  95

Arg His Arg His His Arg Arg Thr Leu Ser Leu Asp Asn Arg Asp Ser
            100                 105                 110

Val Asp Leu Ala Glu Leu Val Pro Ala Val Gly Ala His Pro Arg Ala
        115                 120                 125

Ala Trp Arg Ala Ala Gly Pro Ala Pro Gly His Glu Asp Cys Asn Gly
    130                 135                 140

Arg Met Pro Ser Ile Ala Lys Asp Val Phe Thr Lys Met Gly Asp Arg
145                 150                 155                 160

Gly Asp Arg Gly Glu Asp Glu Glu Glu Ile Asp Tyr Thr Leu Cys Phe
                165                 170                 175

Arg Val Arg Lys Met Ile Asp Val Tyr Lys Pro Asp Trp Cys Glu Val
            180                 185                 190

Arg Glu Asp Trp Ser Val Tyr Leu Phe Ser Pro Glu Asn Arg Phe Arg
        195                 200                 205

Val Leu Cys Gln Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val
    210                 215                 220

Leu Ala Phe Ile Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro
225                 230                 235                 240
```

```
Gln Ile Glu Ala Gly Ser Thr Glu Arg Ile Phe Leu Thr Val Ser Asn
                245                 250                 255

Tyr Ile Phe Thr Ala Ile Phe Val Gly Glu Met Thr Leu Lys Val Val
            260                 265                 270

Ser Leu Gly Leu Tyr Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp
        275                 280                 285

Asn Val Leu Asp Gly Phe Leu Val Phe Val Ser Ile Ile Asp Ile Val
    290                 295                 300

Val Ser Leu Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg
305                 310                 315                 320

Val Leu Arg Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg
                325                 330                 335

Ala Pro Gly Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Lys
            340                 345                 350

Pro Ile Gly Asn Ile Val Leu
        355
```

OPPEDAHL & LARSON

FILE NO. NMED.P-001-2

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My citizenship, residence and post office address are as listed below next to my name.

I believe I am the original, first and [ ] sole/[x]joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: Novel Human Calcium Channels and Related Probes, Cell Lines and Methods
the specification of which

(a) [X] is attached hereto.

(b) [ ] was filed on _____ as Application Serial No. _____ and was amended on _____.

(c) [ ] was described and claimed in International Application No. _____ filed on _____ and amended on _____.

Acknowledgment of Duty of Disclosure

I hereby state that I have reviewed and understood the content of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the patentability of the subject matter claimed in this application in accordance with Title 37, Code of Federal Regulations § 1.56(a).

Continuation-In-Part Application

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status)(patented,pending,abandoned)
09/030,482	February 25, 1999	pending

Power of Attorney

I hereby appoint Carl Oppedahl, PTO Reg. NO. 32,746 and Marrina T. Larson, PTO Reg. No. 32,038 of the firm of OPPEDAHL & LARSON LLP, whose address is PO Box 5270, 611 main Street, Frisco, CO 80443-5270 as attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO:	DIRECT TELEPHONE CALLS TO:
OPPEDAHL & LARSON LLP PO BOX 5270 FRISCO, CO 80443-5270	OPPEDAHL & LARSON (970) 668-2050

OPPEDAHL & LARSON

FILE NO. NMED.P-001-2

Claim for Priority

I hereby claim priority under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have identified any foreign applications for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

EARLIEST FOREIGN APPLICATION(S), FILED WITHIN TWELVE MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION			
COUNTRY APPLICATION NO.	DATE OF FILING (day/month/year)	DATE OF ISSUE (day/month/year)	PRIORITY CLAIMED
			YES[ ] NO[ ]
			YES[ ] NO[ ]
			YES[ ] NO[ ]
FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION			
COUNTRY APPLICATION NO.	DATE OF FILING (day/month/year)	DATE OF ISSUE (day/month/year)	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR	LAST NAME **SNUTCH**	FIRST NAME **TERRY**	MIDDLE NAME **P.**
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE **VANCOUVER**	STATE OR COUNTRY OF RESIDENCE **CANADA**	COUNTRY OF CITIZENSHIP **CANADA**
POST OFFICE ADDRESS **3963 W. 24TH Avenue**		CITY **VANCOUVER**	STATE/COUNTRY ZIP CODE **CANADA V6S 1M1**
DATE July 1, 1999		SIGNATURE	

[X] Signature for additional joint inventor attached. Number of Pages 1.
[ ] Signature by Administrator(trix) or legal representative for deceased or incapacitated inventor. Number of Pages ___.
[ ] Signature for inventor who refuses to sign or cannot be reached by person authorized under 37 CFR § 1.47. Number of Pages ___.

OPPEDAHL & LARSON

FILE NO. NMED.P-001-2

NAME OF SECOND INVENTOR	LAST NAME **BAILLIE**	FIRST NAME **DAVID**	MIDDLE NAME **L.**
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE **VANCOUVER**	STATE OR COUNTRY OF RESIDENCE **CANADA**	COUNTRY OF CITIZENSHIP **CANADA**
POST OFFICE ADDRESS **29 North Kootenay Street**		CITY **VANCOUVER**	STATE/COUNTRY ZIP CODE **CANADA V5K 3P7**
DATE July 1, 1999		SIGNATURE David L Baillie	

NAME OF THIRD INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE	STATE OR COUNTRY OF RESIDENCE	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS		CITY	STATE/COUNTRY ZIP CODE
DATE		SIGNATURE	

NAME OF FOURTH INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE	STATE OR COUNTRY OF RESIDENCE	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS		CITY	STATE/COUNTRY ZIP CODE
DATE		SIGNATURE	

NAME OF FIFTH INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
RESIDENCE & CITIZENSHIP	CITY OF RESIDENCE	STATE OR COUNTRY OF RESIDENCE	COUNTRY OF CITIZENSHIP
POST OFFICE ADDRESS		CITY	STATE/COUNTRY ZIP CODE
DATE		SIGNATURE	